Official Title: A Phase Ib/II Study Evaluating the Safety and Efficacy of Obinutuzumab in Combination With Atezolizumab Plus Polatuzumab Vedotin in Patients With Relapsed or Refractory Follicular Lymphoma and Rituximab in Combination With Atezolizumab Plus Polatuzumab Vedotin in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

NCT Number: NCT02729896

Document Date: Protocol Version 8: 07-November-2018

PROTOCOL

TITLE: A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH ATEZOLIZUMAB PLUS POLATUZUMAB VEDOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA AND RITUXIMAB IN COMBINATION WITH ATEZOLIZUMAB PLUS POLATUZUMAB VEDOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

PROTOCOL NUMBER:	BO29561 **VERSION NUMBER:** 8
EUDRACT NUMBER:	2015-004845-25
IND NUMBER:	128036
TEST PRODUCT:	Obinutuzumab (RO5072759) Rituximab (RO0452294) Atezolizumab (RO5541267) Polatuzumab vedotin (RO5541077)
MEDICAL MONITOR:	[redacted], Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 12 November 2015
DATES AMENDED:	Version 2: 14 January 2016 Version 3: 28 June 2016 Version 4: 17 November 2016 Version 5: 4 May 2017 Version 6: 21 December 2017 Version 7: 1 May 2018 Version 8: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	07-Nov-2018 02:00:10

CONFIDENTIAL

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PROTOCOL AMENDMENT, VERSION 8
RATIONALE

Protocol BO29561 has been amended to include new safety information. Changes to the protocol, along with a rationale for each change, are summarized below:

- Lists of risks for atezolizumab and guidelines for managing patients who experience atezolizumab-associated adverse events have been revised to include nephritis (Sections 5.1.3 and 5.1.7.2 [Table 14]).
- Considering no new safety signals have been identified since protocol amendment Version 7, regular Internal Monitoring Committee assessments will no longer take place and ad hoc meetings maybe called at the discretion of the Medical Monitor in case of newly identified safety signals (Section 3.1.4).
- Post-trial access language was changed allowing patients still under study treatment to enter an extension study in case of earlier closure of Study BO29561 (Section 4.3.4).
- The Medical Monitor information has been updated (Section 5.4.1).
- The survival follow-up period has been added back to Appendices 1 and 2 for the assessment of new anti-lymphoma treatment and survival follow-up. Survival follow-up was removed in error during the previous amendment.
- Appendix 3 has been updated to remove pharmacokinetic sampling one year after the last dose of polatuzumab vedotin. As most of the patients have discontinued study treatment and have not provided this sample, collecting these data from the remaining patients ($n = 3$) will be of limited value.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted], Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IB/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH ATEZOLIZUMAB PLUS POLATUZUMAB VEDOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA AND RITUXIMAB IN COMBINATION WITH ATEZOLIZUMAB PLUS POLATUZUMAB VEDOTIN IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA**
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PHASE:	Phase Ib/II
INDICATION:	Follicular lymphoma or diffuse large B-cell lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of induction treatment consisting of obinutuzumab in combination with atezolizumab plus polatuzumab vedotin (G + Atezo + Pola) in patients with relapsed or refractory FL and rituximab in combination with atezolizumab + polatuzumab vedotin (R + Atezo + Pola) in patients with relapsed or refractory DLBCL, followed by post-induction treatment with G + Atezo (referred to as maintenance) in patients with FL who achieve a CR, a PR, or stable disease at EOI and post-induction treatment with R + Atezo (referred to as consolidation) in patients with DLBCL who achieve a CR or PR at EOI. Specific objectives and corresponding endpoints for the study are outlined below.

In this study, "study treatment" refers to the combination of all study treatment components.

Safety Objective

The safety objectives for this study are as follows:

- To determine the recommended Phase II dose (RP2D) for polatuzumab vedotin when given in combination with fixed doses of obinutuzumab and atezolizumab on the basis of the following endpoint:
- Incidence of DLTs during Cycle 1 and 2 of study treatment
- To evaluate the safety and tolerability of the G + Atezo + Pola treatment group and the R + Atezo + Pola treatment group on the basis of the following endpoints:

  Nature, frequency, severity, and timing of adverse events

  Changes in clinical laboratory results during and following study treatment administration

Efficacy Objective

Response will be determined through use of the positron emission tomography and computed tomography (PET-CT) scans or CT scans alone, using Revised Lugano Response Criteria for Malignant Lymphoma, hereinafter referred to as modified Lugano 2014 criteria. Response will be determined by the investigator.

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of induction treatment with G + Atezo + Pola in relapsed or refractory FL and R + Atezo + Pola in relapsed or refractory DLBCL on the basis of the following endpoint:

- CR at EOI, as determined by the investigator on the basis of PET-CT scans

Secondary Efficacy Objectives

The secondary efficacy objective for this study is to evaluate the efficacy of induction treatment with G + Atezo + Pola and maintenance treatment with G + Atezo in relapsed or refractory FL and of induction treatment with R + Atezo + Pola and consolidation treatment with R + Atezo in relapsed or refractory DLBCL on the basis of the following endpoints:

- CR at EOI, as determined by the investigator on the basis of CT scans alone
- Objective response (defined as a CR or PR) at EOI, as determined by the investigator on the basis of PET-CT scans
- Objective response (defined as a CR or PR) at EOI, as determined by the investigator on the basis of CT scans alone
- Best response of CR or PR during the study, as determined by the investigator on the basis of CT scans alone

Exploratory Efficacy Objectives

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of G + Atezo + Pola on the basis of the following endpoints:

- For patients who have positive PET scans at EOI:
  - CR at 12 months, as determined by the investigator on the basis of PET-CT scans in FL patients
- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause

Pharmacokinetic Objective

The PK objective for this study is to characterize the pharmacokinetics of obinutuzumab, rituximab, atezolizumab, and polatuzumab vedotin when given in combination, on the basis of the following endpoints:

- Observed serum obinutuzumab concentration at specified timepoints
- Observed serum atezolizumab concentration at specified timepoints
- Observed serum and plasma concentrations of polatuzumab vedotin and relevant analytes (total antibody, acMMAE, and unconjugated MMAE) at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab, rituximab, atezolizumab, and polatuzumab vedotin on the basis of the following endpoints:

- Incidence of human anti-human antibodies (HAHAs) to obinutuzumab during the study relative to the prevalence of HAHAs at baseline
- Incidence of human anti-chimeric antibodies (HACAs) to rituximab during the study relative to the prevalence of HACAs at baseline

- Incidence of ATAs to atezolizumab during the study relative to the prevalence of ATAs at baseline
- Incidence of ATAs to polatuzumab vedotin during the study relative to the prevalence of ATAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential effects of HAHAs or ATAs on the basis of the following endpoint:

- Correlation between HAHA or ATA status and efficacy, safety, or PK endpoints

Biomarker Objective

The exploratory biomarker objective for this study is to identify non-inherited biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity, can increase the knowledge and understanding of lymphoma biology or study treatment mechanism of action, or can contribute to improvement of diagnostic assays, on the basis of the following endpoint:

- Association between non-inherited biomarkers and efficacy, safety, pharmacokinetic, or immunogenicity endpoints

Study Design

Description of Study

This Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study will evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of G + Atezo + Pola in patients with relapsed or refractory FL and R + Atezo + Pola in patients with relapsed or refractory DLBCL.

Following the Dear Investigator Letter issued on 1 March 2018, enrollment has been stopped and atezolizumab treatment has been discontinued in all patients still receiving study treatment.

Number of Patients

Overall, it was planned to have 83–92 patients enrolled in this study, at approximately 20 investigative sites around the world. As of 1 March 2018, 13 patients with RR FL and 23 patients with RR DLBCL were enrolled in the study.

Target Population

This study will enroll patients with FL and DLBCL who meet the eligibility criteria presented below.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- For G + Atezo + Pola treatment group: relapsed or refractory FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator
- For R + Atezo + Pola treatment group: relapsed or refractory DLBCL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody, in patients who are not eligible for second line combination (immuno-)chemotherapy and autologous stem-cell transplantation, or who have failed second line combination (immuno-)chemotherapy, or experienced disease progression following autologous stem-cell transplantation
- Histologically documented CD20-positive lymphoma as determined by the local laboratory
- FDG-avid lymphoma (i.e., PET-positive lymphoma)

- At least one bi-dimensionally measurable lesion (>1.5 cm in its largest dimension by CT scan or magnetic resonance imaging [MRI])
- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL

  If archival tissue is unavailable or unacceptable, a pretreatment core-needle, excisional or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

  If the patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, or if the available biopsy was performed more than 6 months prior to Day 1 of Cycle 1 (initiation of study treatment) for patients with DLBCL or more than 12 months prior to Day 1 of Cycle 1 for patients with FL, a core-needle biopsy is strongly recommended.
- 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 or to use single highly effective or combined contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period for ≥ 5 months after the last dose of atezolizumab, ≥ 12 months after the last dose of rituximab, ≥ 12 months after the last dose of polatuzumab vedotin, and ≥ 18 months after the last dose of obinutuzumab.

  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 three months after the last dose of obinutuzumab, rituximab, and atezolizumab, and five months after the last dose of polatuzumab vedotin 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.

<u>Exclusion Criteria</u>

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

- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Known CD20-negative status at relapse or progression
- Central nervous system (CNS) lymphoma or leptomeningeal infiltration
- Prior allogeneic SCT
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1

- Prior standard or investigational anti-cancer therapy as specified below:

  Fludarabine or alemtuzumab within 12 months prior to Day 1 of Cycle 1

  Radioimmunoconjugate within 12 weeks prior to Day 1 of Cycle 1

  Monoclonal antibody or ADC within 4 weeks prior to Day 1 of Cycle 1

  Radiotherapy, chemotherapy, hormonal therapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1

  Anti–PD-1, anti–PD-L1, anti-CTLA4, anti–CD137/41-BB agonist, or anti-CD40 agonist antibodies
- Clinically significant toxicity (other than alopecia) from prior treatment that has not resolved to Grade $\leq$2 (per NCI CTCAE v4.0) prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medications, including, but not limited to, prednisone, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor agents within 2 weeks prior to Day 1 of Cycle 1

  Treatment with inhaled corticosteroids and mineralocorticoids is permitted.

  If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg of prednisone or equivalent can be given for a maximum of 5 days, but all tumor assessments must be completed prior to initiation of corticosteroid treatment.
- History of solid organ transplantation
- History of severe allergic or anaphylactic reaction to humanized, chimeric, or murine monoclonal antibodies
- Known hypersensitivity or allergy to murine products
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab, obinutuzumab, rituximab, or polatuzumab vedotin formulations
- Known history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis or evidence of active pneumonitis on screening chest CT scan.

  History of radiation pneumonitis in the radiation field (fibrosis) is allowed.
- Active bacterial, viral, fungal, or other infection or any major episode of infection requiring treatment with IV antibiotics within 4 weeks of Day 1 of Cycle 1

  Caution should be exercised when considering the use of obinutuzumab and rituximab in patients with a history of recurring or chronic infections.
- Receipt of oral or intravenous antibiotics for treatment of serious infections within 4 weeks prior to Day 1 of Cycle 1
- Positive for hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at screening
- Known history of HIV positive status

  For patients with unknown HIV status, HIV testing will be performed at screening if required by local regulations.
- History of PML
- Vaccination with a live virus vaccine or live attenuated vaccine within 28 days prior to Day 1 of Cycle 1, or anticipation that such a live, attenuated vaccine will be required during the study
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:

  Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer

Any previously treated malignancy that has been in remission without treatment for ≥ 2 years prior to enrollment

- History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study.

  Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.
- Grade > 1 peripheral neuropathy present at screening
- Evidence of any significant, uncontrolled concomitant disease 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 previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm)
- Major surgical procedure other than for diagnosis within 28 days prior to Day 1 of Cycle 1, or anticipation of a major surgical procedure during the course of the study
- Inadequate hematologic function (unless due to underlying lymphoma), defined as follows:

  Hemoglobin < 9 g/dL

  ANC $< 1.5 \times 10^9$/L

  Platelet count $< 75 \times 10^9$/L
- Inadequate liver function defined as follows (unless due to underlying lymphoma):

  For patients enrolled in the dose escalation:

  AST $>$ ULN or serum total bilirubin $>$ULN

  For patients enrolled in the expansion phase:

  AST or ALT $> 2.5 \times$ ULN

  Serum total bilirubin $> 1.5 \times$ ULN (or $> 3 \times$ ULN for patients with Gilbert syndrome)
- Any of the following abnormal laboratory values (unless due to underlying lymphoma):

  Creatinine $>$1.5 times the upper limit of normal (ULN) (unless creatinine clearance is normal) or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)

  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
- Pregnant or lactating, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to Day 1 of Cycle 1.
- Life expectancy < 3 months
- Unable to comply with the study protocol, in the investigator's judgment

End of Study

The end of this study is defined as the time when all enrolled patients with FL and all enrolled patients with DLBCL have completed the 90-day safety follow-up visit, following completion or premature discontinuation of study treatment.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Dosing with atezolizumab has been discontinued in all patients.

Obinutuzumab

Obinutuzumab will be supplied by the Sponsor as an investigational medicinal product (IMP). Obinutuzumab will be provided as a single-dose, sterile liquid formulation in a 50-mL glass vial containing 1000 mg/40 mL of obinutuzumab. In addition to the drug substance, the liquid is also composed of histidine, trehalose, and poloxamer 188. For information on the formulation and handling of obinutuzumab, see the obinutuzumab Investigator's Brochure and the Pharmacy Manual.

Atezolizumab

Atezolizumab was supplied by the Sponsor as an IMP. Atezolizumab Drug Product is provided in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume. Extraction of 14 mL of atezolizumab solution will contain an 840-mg dose. For information on the formulation and handling of atezolizumab, see the atezolizumab Investigator's Brochure and the Pharmacy Manual.

Polatuzumab Vedotin

Polatuzumab vedotin will be supplied by the Sponsor as an IMP. Polatuzumab vedotin will be provided as a sterile, white to off-white, preservative-free lyophilisate in single-use vials. For information on the formulation and handling of polatuzumab vedotin, see the polatuzumab vedotin Investigator's Brochure and the Pharmacy Manual.

Rituximab

Rituximab will be supplied by the Sponsor as an IMP. Rituximab is packaged in 10-mL (100-mg) and 50-mL (500-mg) single-dose, pharmaceutical-grade glass vials at a concentration of 10 mg/mL of protein. The antibody is formulated for IV injection as a sterile product in a solution of sodium chloride (pH 6.5) containing polysorbate 80 and sodium citrate. For information on the formulation and handling of rituximab, see the Rituximab Investigator's Brochure and the Rituximab Pharmacy Manual.

Statistical Methods

Efficacy Analyses

The primary and secondary efficacy analyses will include all patients enrolled in the expansion phase, and will be performed by treatment group. In addition, patients with FL who received polatuzumab vedotin at the RP2D during the dose-escalation phase will be pooled for analysis with patients with FL treated in the expansion phase. Patients with DLBCL from the safety run-in phase will be pooled for analysis with patients with DLBCL treated in the expansion phase at the same polatuzumab vedotin dose.

Determination of Sample Size

Limited dose-finding will be conducted during the dose-escalation phase of polatuzumab vedotin in combination with obinutuzumab and atezolizumab. The estimated sample size follows from the dose-escalation rules for a standard 3+3 algorithm. A total of 9 patients with RR FL were enrolled in the dose-escalation phase (3 patients in the Pola 1.4-mg dose cohort and 6 patients in the Pola 1.8-mg dose cohort), and a total of 7 patients with RR DLBCL were enrolled into the safety run-in phase and treated with 1.8 mg polatuzumab vedotin. During the expansion phase, 34–40 patients with DLBCL and 34–37 patients with FL (for a total of 40 patients with FL at RP2D in the dose-escalation and expansion phases) were planned to be enrolled. Overall, approximately 83–92 patients were planned to be enrolled in the study. As of 1 March 2018, 13 patients with RR FL and 23 patients with RR DLBCL were enrolled in the study.

The primary efficacy analysis will be the estimation of the true proportion of patients expected to obtain a PET-CT–defined CR at EOI.

Interim Analyses

No interim analyses are planned and review of safety and/or efficacy data by the Internal Monitoring Committee may be requested by and carried out at the discretion of the Medical Monitor. Further details regarding the rules and guidelines of data review will be provided in an IMC charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	activated B cell-like (subgroup)
acMMAE	antibody-conjugated MMAE
ADC	antibody-drug conjugate
ALP	alkaline phosphatase
ATA	anti-therapeutic antibody
Atezo	atezolizumab
BSA	body surface area
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRO	contract research organization
CT	computed tomography
C_{trough}	trough concentration
CVP	cyclophosphamide, vincristine, and prednisone
DHAP	dexamethasone, cytosine arabinoside, and cisplatin
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EOI	end of induction
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
FLIPI, FLIPI2	Follicular Lymphoma International Prognostic Index Follicular Lymphoma International Prognostic Index 2
G	obinutuzumab (GA101)
GCB	germinal-center B cell–like (subgroup)
GCP	Good Clinical Practice

Abbreviation	Definition
G-CSF	granulocyte colony-stimulating factor
GEP	gene expression profile
GFP	green fluorescent protein
GI	gastrointestinal
HAHA	human anti-human antibody
HACA	human anti-chimeric antibody
HbA_{1c}	glycosylated hemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	Hodgkin's disease
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
ICE	ifosfamide, carboplatin, and etoposide
ICH	International Conference on Harmonisation
IFN-α	interferon alpha
IFN-γ	interferon gamma
IL	interleukin
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IPI	International Prognostic Index
irAE	immune-related adverse event
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous
IxRS	interactive voice or web-based response system
LMWH	low-molecular-weight heparin
Lugano 2014 criteria	Lugano Response Criteria for Malignant Lymphoma
MCL	Mantle cell lymphoma
MRD	minimal residual disease
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma

Abbreviation	Definition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
NHL	non-Hodgkin's lymphoma
NK cells	natural killer cells
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
Pola	polatuzumab vedotin
PR	partial response
q2w	every 2 weeks
Q3W	every 3 weeks
q4w	every 4 weeks
R	rituximab
RR	relapsed/refractory
RANKL	Receptor activator of nuclear factor kappa-B ligand
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
SCID	severe compromised immunodeficient
SCT	stem-cell transplantation
SJS	Stevens-Johnson syndrome
TAb	Total antibody
TEN	toxic epidermal necrolysis
TFH	Follicular helper T cells
TIL	tumor-infiltrating lymphocyte
TLS	tumor lysis syndrome
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma (NHL) is the most common hematologic malignancy in adults. In 2013, there were an estimated 69,740 new cases and 19,020 deaths due to the disease in the United States (Siegel et al. 2013). In Europe, there were an estimated 93,400 new cases and 37,900 deaths in 2012 (Ferlay et al. 2013). Non-Hodgkin's lymphoma is most often of B-cell origin, including a wide range of different subtypes of B-cell lymphoma, broadly divided into indolent and aggressive lymphomas, each with unique characteristics.

1.1.1 Follicular Lymphoma

Indolent B-cell lymphomas 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 B-cell lymphoma, accounting for about 22% of all newly diagnosed cases of NHL (Armitage and Weisenburger 1998). Approximately 90% of the cases have at (14;18) translocation, which juxtaposes *BCL2* with the IgH locus and results in overexpression of the anti-apoptotic protein, *BCL2*.

Despite therapies currently available, FL remains an incurable disease. The addition of rituximab, an anti-CD20 monoclonal antibody, to commonly used induction chemotherapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone CHOP (CHOP cyclophosphamide, doxorubicin, vincristine, and prednisone), cyclophosphamide, vincristine, and prednisone CVP (CVP cyclophosphamide, vincristine, and prednisone); fludarabine, or bendamustine (Dreyling et al. 2014; Zelenetz et al. 2013), followed by rituximab maintenance therapy led to prolonged remission and improved patient outcomes. Updated results from Study MO18264 confirmed the benefit of 2-year rituximab maintenance in patients responding to first-line immunotherapy, with a 6-year progression-free survival (PFS) of 59.2% compared with 42.7% in the observation arm ($p < 0.0001$) (Salles et al. 2013).

Despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, most patients will eventually experience disease relapse. Relapses are characterized by increasing refractoriness and decreasing duration of response to subsequent lines of therapy. Thus, new treatments are needed to improve the outcome 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 NHLs diagnosed annually (Armitage and Weisenburger 1998). The use of immunochemotherapy, most commonly rituximab + CHOP (R-CHOP) for newly diagnosed DLBCL, led to a significant improvement in survival in patients in all age groups. In older patients (> 60 years of age), R-CHOP was associated with a 2-year event-free survival (EFS) rate of 57% and a

10-year survival rate of 43.5% (Coiffier et al. 2010). In younger patients (18–60 years of age) with favorable prognostic features, R-CHOP demonstrated a 3-year EFS rate of 79% and a survival rate at 3 and 6 years of 93% and 74.3%, respectively (Pfreundschuh et al. 2011). However, nearly 40% of patients with DLBCL will eventually die of relapsed disease or disease that is refractory to first-line treatment. Patients with a high-risk International Prognostic Index (IPI) have a 5-year PFS rate of only 40% following treatment with R-CHOP (Zhou et al. 2014).

Second-line treatments consist of high-dose chemotherapy regimens such as rituximab + ifosfamide, carboplatin, and etoposide (R-ICE) or rituximab + dexamethasone, cytosine arabinoside, and cisplatin (R-DHAP) followed by autologous stem-cell transplantation (SCT). Approximately half of the patients do not achieve a complete remission after salvage treatment (Gisselbrecht et al. 2010). Moreover, elderly patients or patients with comorbidities are often deemed ineligible for this aggressive therapy.

Specific molecular subsets of DLBCL are associated with an inferior outcome following R-CHOP therapy. Germinal center B cell–like (GCB) DLBCL had a better prognosis than activated (non-germinal) B cell–like (ABC) DLBCL, with a 3-year survival rate of 84% versus 56%, respectively ($p < 0.001$) (Lenz et al. 2008). Several genetic abnormalities predictive of poor outcome have been identified in DLBCL, including *MYC* rearrangement, *BCL2* and *BCL6* overexpression, and *TP53* mutations. Rearrangement in *MYC* (*MYC*-positive DLBCL) has been reported in 9%–17% of DLBCL cases and often correlates with the GCB DLBCL phenotype (Savage et al. 2009; Barrans et al. 2010). The DLBCL treated with R-CHOP has a markedly worse 5-year survival rate in patients with *MYC*-positive DLBCL compared with *MYC*-negative DLBCL (33% vs. 72%) (Savage et al. 2009). Concurrent *MYC* and *IGH-BCL2* rearrangement ("double-hit" DLBCL), observed in 2%–11% of patients with DLBCL, represents a DLBCL subset with an inferior outcome (5-year PFS of 18%; 5-year survival of 27%) (Savage et al. 2009; Dunleavy et al. 2014). Mutations in *TP53* have been described in approximately 20% of patients with DLBCL and are strong predictors of poor overall survival (Young et al. 2008; Xu-Monette et al. 2012).

The DLBCL remains a disease with high unmet medical need. Novel targeted therapies are needed to move treatment options beyond R-CHOP.

1.2 BACKGROUND ON OBINUTUZUMAB

Obinutuzumab is a novel glycoengineered type II anti-CD20 antibody. Compared with rituximab, obinutuzumab is characterized by more potent direct B-cell death induction and increased affinity for FcγRIII receptors expressed on natural killer (NK) cells, macrophages, and monocytes, resulting in enhanced antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis (Beers et al. 2010; Mössner et al. 2010; Herter et al. 2014). Together, these characteristics confer obinutuzumab with enhanced immune effector functions and B-cell-depleting activity compared with rituximab.

Obinutuzumab is approved for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). Obinutuzumab is also approved for use in combination with bendamustine followed by obinutuzumab maintenance for the treatment of patients with FL who did not respond to or who progressed during or after treatment with rituximab or a rituximab-containing regimen and in combination with chemotherapy, followed by obinutuzumab maintenance for the treatment of patients with previously untreated follicular lymphoma, in the United States, Europe, and many other countries. Obinutuzumab continues to be investigated in a large clinical program.

1.2.1 Nonclinical Studies with Obinutuzumab

In nonclinical studies, obinutuzumab demonstrated superior depletion of normal B cells (measured as $CD19^+$ depletion) from the blood of healthy volunteers (Mössner et al. 2010) and of malignant B cells from the blood of patients with CLL (Patz et al. 2011). Nonclinical xenograft experiments performed with obinutuzumab as monotherapy and in combination with chemotherapy have consistently showed that obinutuzumab has promising anti-tumor activity (Mössner et al. 2010; Dalle et al. 2011) and have demonstrated the superiority of obinutuzumab over rituximab (Herting et al. 2014).

For more detailed nonclinical information on obinutuzumab, refer to the Obinutuzumab Investigator's Brochure.

1.2.2 Clinical Studies with Obinutuzumab

Obinutuzumab is being studied in patients with CLL, indolent and aggressive NHL, and solid tumors. Available efficacy results from the NHL cohorts in these studies and available safety results from all patients are summarized below.

For more detailed clinical information on obinutuzumab, including results in the CLL cohorts of the clinical studies and clinical pharmacology data, please refer to the Obinutuzumab Investigator's Brochure.

1.2.2.1 Clinical Safety of Obinutuzumab

As of 31 October 2017, 4981 patients have received obinutuzumab via clinical trial participation. Patients with NHL (including DLBCL, indolent B-cell lymphoma, and CLL) have been treated with obinutuzumab given as monotherapy or in combination with CHOP, bendamustine, FC, or chlorambucil, at doses ranging from 50–2000 mg. Overall, the safety of obinutuzumab monotherapy and obinutuzumab combination therapy was manageable.

The most frequent causes of death were disease progression and adverse events associated with infectious diseases. This is consistent with the study population and the disease under treatment. The incidence of fatal adverse events was similar across all ongoing trials. In Study GAO4768g (obinutuzumab 1000 mg vs. 2000 mg), the

incidence of deaths did not increase with increased obinutuzumab dose (7.5% and 2.6%, respectively).

Of particular interest, a high incidence of infusion-related reactions (IRRs) was observed consistently in all obinutuzumab trials. The reported incidence of IRRs varied across studies. The incidence of IRRs in relapsed or refractory patients receiving obinutuzumab monotherapy was 100% in CLL (n = 38) and 82.4% in NHL (n = 205) in Studies BO21003 and BO20999 (pooled data). Anaphylaxis has also been reported in patients treated with obinutuzumab.

Other important risks associated or potentially associated with obinutuzumab are tumor lysis syndrome (TLS), neutropenia (including prolonged and late-onset neutropenia), thrombocytopenia (including acute thrombocytopenia), infections (including progressive multifocal leukoencephalopathy [PML] and hepatitis B virus [HBV] reactivation), prolonged B-cell depletion, impaired immunization response, worsening of preexisting cardiac conditions, gastrointestinal (GI) perforation, immunogenicity, and second malignancies. The important identified risks associated with obinutuzumab are presented in detail in Section 5.1.1 and in the obinutuzumab Investigator's Brochure.

1.2.2.2 Clinical Pharmacokinetics of Obinutuzumab

On the basis of available pharmaockinetic (PK) data, a two-compartment PK model comprising both a linear clearance pathway and a non-linear time-varying clearance pathway adequately describes serum obinutuzumab concentration data. The initial clearance of obinutuzumab is $> 2 \times$ higher than the steady-state clearance, consistent with a decrease in the time-varying clearance component, which is high at the start of treatment and declines with repeated cycles of obinutuzumab treatment. The time-varying clearance pathway is consistent with target-mediated drug disposition, such that at the start of treatment, there is a large quantity of CD20-positive cells that rapidly bind to obinutuzumab. Repeated dosing with obinutuzumab saturates the pool of CD20-positive cells, hence reducing this component in clearance. The linear clearance pathway is consistent with catabolism of IgG antibodies and is therefore independent of CD20-positive cells. Refer to the Obinutuzumab Investigator's Brochure for additional details.

1.2.2.3 Clinical Efficacy of Obinutuzumab in Patients with Non-Hodgkin's Lymphoma

In studies of obinutuzumab monotherapy in patients with relapsed or refractory NHL (studies BO20999, BO21003, YP25623, and JO21900), the proportion of patients who had a response (complete response [CR] or partial response [PR]) at the end of treatment (as determined on the basis of computed tomography [CT] scans alone) ranged from 28% to 58%. The CR rate ranged from 0% to 19%.

In early studies of obinutuzumab in combination with chemotherapy (e.g., CHOP, FC, or bendamustine) in patients with previously untreated or relapsed or refractory NHL

(studies BO21000, GAO4915g, and GAO4753g), the proportion of patients with a CR or PR at the end of induction (EOI) treatment ranged from 69% to 96%. The CR rate with combination therapy was 35%–39% in patients with previously untreated FL, 11%–50% in patients with relapsed or refractory indolent NHL, and 55% in patients with previously untreated DLBCL.

A Phase III study, GAO4753g, investigated obinutuzumab + bendamustine (G-benda) compared with bendamustine alone in patients with rituximab-refractory indolent NHL (n = 396). Patients in the G-benda arm who had not experienced disease progression at the end of induction received obinutuzumab monotherapy every 2 months for up to 2 years. On the basis of positive results from this study, demonstrating significant improvement in PFS in the G-benda arm, with a median investigator-assessed PFS of 29 versus 14 months (hazard ratio [HR]: 0.52; 95% CI: 0.39, 0.70; $p < 0.0001$) (Sehn et al. 2015), obinutuzumab was granted approval for use in patients with FL who did not respond to or who progressed during or after treatment with rituximab or a rituximab-containing regimen (see Section 1.2).

A Phase III study, BO21223, investigated obinutuzumab + chemotherapy (G-benda, G-CVP, G-CHOP) compared with rituximab + chemotherapy followed by obinutuzumab or rituximab maintenance in patients with previously untreated indolent NHL (FL cohort, n = 1202). On the basis of positive results that demonstrated significant improvement in PFS in the obinutuzumab chemotherapy arm (stratified HR INV PFS 0.66 [95% CI: 0.51 to 0.85; p = 0.0012]), the Independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor at a pre-planned interim analysis (Marcus et al. 2017).

A Phase III study, BO21005, investigated obinutuzumab + CHOP (G-CHOP) compared with rituximab + CHOP (R-CHOP) in patients with previously untreated DLBCL. The study did not meet its primary endpoint of PFS at final analysis. Based upon the BO21005 efficacy results, this study protocol is amended (version 4) to cease evaluating obinutuzumab in patients with relapsed or refractory DLBCL; these patients will receive instead atezolizumab in combination with rituximab and polatuzumab vedotin.

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits its interaction with its receptors, PD-1 and B7-1 (also known as CD80). Both of these interactions are reported to provide inhibitory signals to T cells. Therapeutic blockage of PD-L1 binding by atezolizumab is expected to enhance the magnitude and quality of the tumor-specific T-cell responses, resulting in improved anti-tumor activity. Atezolizumab was engineered to impair its binding to Fc receptors, thus eliminating detectable FC-effector function and associated antibody-mediated clearance of activated effector T cells (Teffs).

Atezolizumab is approved for the treatment of patients with locally advanced or metastatic urothelial cancer who (1) have disease progression during or following platinum-containing chemotherapy or (2) have disease progression within 12 months of neoadjudvant or adjuvant treatment with platinum-containing chemotherapy. Atezolizumab is also approved for patients with metastatic non-small cell lung cancer who have disease progression during or following platinum-containing chemotherapy. Atezolizumab is being investigated as a potential treatment in multiple solid tumors and hematologic malignancies in humans.

1.3.1 Nonclinical Studies with Atezolizumab

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab. Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies and provided adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway. Improved immune responses and the potential to increase immune-associated inflammatory lesions were identified as possible safety risks in patients.

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

1.3.2 Clinical Studies with Atezolizumab

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies. The majority of the safety and efficacy data summarized below are from Phase Ia Study PCD4989g, a multicenter, first-in-human, open-label, dose-escalation trial evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics (PD), and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 3 weeks (Q3W) to patients with locally advanced or metastatic solid tumors or hematologic malignancy.

1.3.2.1 Summary of Clinical Safety of Atezolizumab

The safety data for atezolizumab have been derived from Study PCD4989g, in which atezolizumab is being used as single-agent therapy in patients with locally advanced or metastatic solid tumors or hematologic malignancies. As of the data cutoff date of 15 December 2015, the clinical database contained preliminary safety data from 629 patients who received atezolizumab at doses ranging from 0.01–20 mg/kg across multiple tumor types. No dose-limiting toxicities have been observed at any dose level, no maximum tolerated dose and no clear dose related trends in the incidence of adverse events have been determined.

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications.

Summary of Adverse Events

Adverse events were reported in 619 of the 629 safety-evaluable patients (98.4%). Adverse events occurring in ≥10% of treated patients included fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, anemia, vomiting, asthenia, back pain, headache, arthralgia, pruritus, rash, abdominal pain, insomnia, peripheral edema, urinary tract infection, dizziness, and chills. Grade ≥3 adverse events were reported in approximately 43% of patients.

Treatment-related adverse events (per investigator's assessment of causality) were reported in 444 of 629 (70.6%) patients. Grade 3–4 treatment-related events occurring in ≥5 patients (≥0.8%) were reported in 13.7% of patients, with fatigue and asthenia (1.3% each), AST increased and dyspnea (1.1% each), and hyponatremia (0.8%).

Serious adverse events (SAEs) have been reported in 261 of 629 patients (41.5%) in Study PCD4989g. Reported SAEs were consistent with the underlying disease. Treatment-related SAEs were reported in 9.1% of patients. Atezolizumab-related SAEs occurring in ≥2 patients (≥0.3%) were pyrexia (2.1%); dyspnea (0.8%); pneumonitis (0.6%); fatigue, malaise, hypoxia, and colitis (0.5% each); and bone pain (0.3%).

Ten patients (1.6%) had Grade 5 events. The three events assessed by the investigator as related to atezolizumab were death (not otherwise specified), hepatic failure, and pulmonary hypertension.

Additional details for each case are provided in the Atezolizumab Investigator's Brochure.

Immune-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation or immune related adverse events have been closely monitored during the atezolizumab clinical program. To date, immune-related adverse events associated with atezolizumab include pneumonitis, hepatitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, and myocarditis.

Guidelines for the management of potential immune related adverse events are described in Section 5.1.6.

Refer to the Atezolizumab Investigator's Brochure for details on immune related adverse events observed in patients treated with atezolizumab. Guidelines for the management of immune related adverse events are described in the Atezolizumab Investigator's Brochure.

1.3.2.2 Clinical Pharmacokinetics of Atezolizumab

On the basis of available preliminary PK data (for doses ranging from 0.03–20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses $\geq$ 1 mg/kg. Serum atezolizumab concentrations exhibited a biphasic disposition with an initial rapid distribution phase followed by a slow elimination phase. For the 1 mg/kg and 20 mg/kg dose groups, the mean apparent clearance (CL) ranged from 3.50–3.55 mL/day/kg and the mean volume of distribution at steady state (V_{ss}) ranged from 48–65.7 mL/kg, which are consistent with the expected profile of an IgG1 antibody in humans. Atezolizumab exhibited non-linear pharmacokinetics at doses of $<$ 1 mg/kg (i.e., 0.03–0.3 mg/kg), which is likely due to target-mediated clearance at lower concentrations.

The development of anti-therapeutic antibodies (ATAs) has been observed in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses ranging from 10–20 mg/kg. Patients treated with atezolizumab at 10, 15, and 20 mg/kg have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between the detection of ATAs and adverse events or infusion reactions has been observed.

Please refer to the atezolizumab Investigator's Brochure for details on clinical pharmacokinetics and immunogenicity.

1.3.2.3 Summary of Clinical Activity of Atezolizumab

Patients with multiple tumor types were included in Study PCD4989g, with the largest cohorts consisting of patients with non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and urothelial bladder cancer (UBC). Clinical activity of atezolizumab monotherapy was observed in a broad range of malignancies, including NSCLC, RCC, melanoma, bladder cancer, colorectal cancer, head and neck cancer, gastric cancer, breast cancer and sarcoma. Analyses of response by PD-L1 expression status in tumor-infiltrating immune cells (ICs) and tumor cells (TCs) in baseline tumor tissue were also conducted.

Efficacy results, based on a data cutoff date of 15 December 2015, are summarized below for patients with hematologic malignancies. Please see the Atezolizumab Investigator's Brochure for clinical activity of single-agent atezolizumab and in combination studies in solid tumors.

Eleven patients with refractory or relapsed hematologic malignancies have been treated with atezolizumab in Study PCD4989g. This includes patients with multiple myeloma (n=4), FL (n=3), cutaneous T-cell lymphoma (n=2), DLBCL (n=1), and Hodgkin's lymphoma (n=1). Among the 10 patients who were evaluable for response, the best response was PR for the 2 patients with cutaneous T-cell lymphoma; stable disease for the 3 patients with FL, the 1 patient with Hodgkin's lymphoma, and 2 patients with multiple myeloma; and progressive disease for the remaining 2 patients with multiple myeloma.

1.4 BACKGROUND ON POLATUZUMAB VEDOTIN

Polatuzumab vedotin (DCDS4501A) is an antibody–drug conjugate (ADC) consisting of a humanized IgG1 anti–human CD79b monoclonal antibody (MCDS4409A) and a potent anti-mitotic agent, mono-methyl auristatin E (MMAE), linked through a protease-labile linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl.

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

The MMAE has a mode of action that is 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. The MMAE then binds to tubulin and inhibits microtubule polymerization, 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, the cytotoxic activity of MMAE, and the increased potency of MMAE compared with vincristine.

Polatuzumab vedotin is being investigated as a potential treatment against hematologic malignancies in humans.

1.4.1 Nonclinical Studies with Polatuzumab Vedotin

Comprehensive pharmacologic, pharmacokinetic, pharmacodynamic, and toxicology 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 cynomolgus monkeys, rats, or mice—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 displayed potent and selective inhibition of tumor cell proliferation

in vitro. Polatuzumab vedotin demonstrated activity in nonclinical murine xenograft models of human CD79b-positive B-cell lymphoma. Additionally, when combined with rituximab + chemotherapy (i.e., cyclophosphamide, doxorubicin, and prednisone [CHP] or bendamustine), polatuzumab vedotin demonstrated superior anti-tumor activity in xenograft models of B-cell lymphoma when compared with polatuzumab vedotin as a single agent or in combination with standard immunochemotherapy (Dornan et al. 2009). 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. In both monkeys and rats, the predominant antigen-independent findings associated with exposure to polatuzumab vedotin or the surrogate ADC were reversible bone marrow toxicity and associated peripheral blood cell effects, likely related to the pharmacologic activity of MMAE. The PK profiles of polatuzumab vedotin and the surrogate ADC suggested that the pharmacokinetics of the ADC were driven mainly by the antibody component (similar serum concentration–time profile between the ADC and total monoclonal antibody).

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

1.4.2 Clinical Studies with Polatuzumab Vedotin

Clinical data on polatuzumab vedotin are available from one completed Phase I/Ib study (DCS4968g), and the ongoing Phase Ib/II studies GO27834, GO29044 and GO29365 in patients with B-cell lymphoma.

Available safety and efficacy data from these studies are summarized in Sections 1.4.2.1 and 1.4.2.3, respectively. Preliminary safety data from 39 patients receiving polatuzumab vedotin in combination with obinutuzumab in Study GO27834; from 21 patients receiving polatuzumab vedotin in combination with rituximab + bendamustine and 28 patients receiving polatuzumab vedotin in combination with obinutuzumab + bendamustine in an ongoing Phase Ib/II study (GO29365); and from 39 patients receiving polatuzumab vedotin in combination with rituximab + CHP and 14 patients receiving polatuzumab vedotin in combination with obinutuzumab + CHP in the ongoing Phase Ib/II study (GO29044) are summarized in Section 1.5.4.3. Limited safety data from 7 patients receiving single-agent polatuzumab vedotin in an ongoing Phase I study (JO29138) are provided in the polatuzumab vedotin Investigator's Brochure.

Refer to the Polatuzumab Vedotin Investigator's Brochure for more details on clinical information, including clinical pharmacology data.

1.4.2.1 Clinical Safety of Polatuzumab Vedotin

Clinical safety data are provided for 280 patients with B-cell lymphoma or CLL who received polatuzumab vedotin as a single agent (Study DCS4968g), in combination with

rituximab (Studies DCS4968g and GO27834), in combination with rituximab + CHP (Study GO29044), or in combination with rituximab + bendamustine (Study GO29365).

In Study DCS4968g, Grade ≥ 3 adverse events were reported in 50 of 68 patients (74%) with B-cell lymphoma (indolent B-cell lymphoma, DLBCL, and mantle cell lymphoma [MCL]) who received single-agent polatuzumab vedotin; the most common events (≥ 10% of patients) were neutropenia (38%) and anemia (9%). Grade ≥ 3 adverse events were reported in 13 of 18 patients (72%) with CLL who received single-agent polatuzumab vedotin; the most common events (≥ 10% of patients) were neutropenia (17%) and diarrhea, anemia, hyponatremia, febrile neutropenia, and fatigue (11%). The SAEs were reported in 35 of 86 patients. The most frequently reported SAEs among the 95 patients treated with polatuzumab vedotin alone (n = 86) or in combination with rituximab (n = 9) were febrile neutropenia, pyrexia, and lung infection (4% each), followed by diarrhea and peripheral sensory neuropathy (3% each).

The overall safety profile of polatuzumab vedotin in combination with rituximab was similar to that of single-agent polatuzumab vedotin. In Study DCS4968g, Grade ≥ 3 adverse events were reported in 7 of 9 patients (78%) with B-cell lymphoma; the most common events (2 or more patients) were neutropenia (5 patients) and anemia and febrile neutropenia (2 patients each). The SAE were reported in 5 of 9 patients (56%). In Study GO27834, Grade ≥ 3 adverse events were reported in 51 of 79 patients (65%) with B-cell lymphoma; the most common events (≥ 5% of patients) were neutropenia (24%), diarrhea (8%), febrile neutropenia (5%), and dyspnea (5%). The SAEs were reported in 28 of 79 patients (35%), with febrile neutropenia being the most frequently reported (6%).

In Study GO29365, Grade ≥ 3 adverse events were reported in 11 of 21 patients (52%) with B-cell lymphoma who received polatuzumab vedotin in combination with rituximab plus bendamustine. The most frequent events (≥ 10% of patients) were nausea (43%), diarrhea (38%) and fatigue (43%).

In Study GO29044, Grade ≥ 3 adverse events were reported in 18 of 39 patients (46%) with B-cell lymphoma who received polatuzumab vedotin in combination with rituximab plus CHP. The most frequent events (≥ 10% of patients) were fatigue 39, nausea (36%), and diarrhea (33%).

A total of 38 deaths have been reported: 11 deaths in patients treated with single-agent polatuzumab vedotin and 27 in patients treated with polatuzumab vedotin combined with rituximab. The majority of deaths were judged as related to disease progression, and none of the deaths were judged as related to polatuzumab vedotin.

1.4.2.2 Clinical Pharmacokinetics of Polatuzumab Vedotin

The pharmacokinetics of antibody-conjugated MMAE (acMMAE), total antibody (TAb), and unconjugated MMAE appear to be dose-proportional across the dose range of

0.1–2.4 mg/kg of polatuzumab vedotin. At the 2.4 mg/kg dose, mean half-life values ranged from 5.2–6.3 days for acMMAE and from 6.2–8.1 days for TAb. Mean CL values ranged from 16.2–23.8 mL/day/kg for acMMAE and from 11.4 to 28.0 mL/day/kg for TAb, which suggests that the disposition of acMMAE, as characterized by a small steady-state volume of distribution and slow clearance, is largely dominated by its antibody component. Across doses tested (0.1–2.4 mg/kg), the exposure of acMMAE was higher than that of unconjugated MMAE, with acMMAE having 100- to 150-fold higher C_{max} values and 50-fold higher AUC_{inf} values. MMAE peak concentrations were reached 2–3 days after dosing. The mean half-life for unconjugated MMAE was 2.9–6.4 days, which is similar to the corresponding value for acMMAE and suggestive of formation rate–limited kinetics of unconjugated MMAE due to the ADC catabolism. Combination with the anti-CD20 antibody rituximab does not appear to affect the pharmaockinetics of acMMAE, TAb, or unconjugated MMAE in the relapsed or refractory B-cell lymphoma patient population.

1.4.2.3 Clinical Activity of Polatuzumab Vedotin

Clinical activity data are provided below for patients receiving polatuzumab vedotin as a single agent in Study DCS4968g and in combination with rituximab in studies DCS4968g and GO27834. In both studies, patients received treatment Q3W until progression or unacceptable toxicity, for up to 1 year.

Polatuzumab vedotin demonstrated clinical activity when given as a single agent to patients with relapsed or refractory disease in Study DCS4968g. At the highest dose of 2.4 mg/kg, objective responses (CR or PR) were observed in 7 of 16 (44%) patients with indolent B-cell lymphoma and 14 of 27 (52%) patients with DLBCL. At a dose of 1.8 mg/kg, a PR was observed in 2 of 4 patients with DLBCL and in 2 of 2 patients with MCL, and no objective responses were observed in the 5 patients with CLL. At the data cutoff date, the median duration of response was 6.2 months (95% CI: 3.3, 19.3 months) for the 2.4 mg/kg dose and 6.6 months (95% CI: 2.3, 11.4 months) for the 1.8 mg/kg dose. At the 2.4 mg/kg dose, median PFS was 7.9 months (95% CI: 3.0, 11.6 months) for patients with indolent B-cell lymphoma and 5.0 months (95% CI: 2.3, 6.8 months) for patients with DLBCL. Median PFS was 4.6 months (95% CI: 1.4, 13.9 months) for patients with DLBCL treated at the 1.8 mg/kg dose.

Polatuzumab vedotin also demonstrated clinical activity when administered in combination with rituximab in patients with relapsed or refractory indolent or aggressive B-cell lymphoma (Study DCS4968g); in combination with rituximab and bendamustine in patients with relapsed or refractory FL or DLBCL (Study GO29365); and in combination with and CHP in patients with relapsed or refractory B-cell lymphoma or previously untreated DLBCL (Study GO29044). Preliminary results from these studies are presented in Section 1.5.4.3.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Despite significant therapeutic progress with the addition of rituximab to chemotherapy for first-line treatment of patients with B-cell NHL, FL and DLBCL remain an area of high medical need in which novel targeted therapies are required to improve patient outcome (see Section 1.1). Patients ultimately relapse, and subsequent active and well-tolerated therapies are needed. Emerging evidence of the activity of new drugs that target tumor-associated cell-surface antigens (e.g., monoclonal antibodies), tumor microenvironment, and checkpoint inhibitors that target the PD-1/PD-L1 axis opens the way to more targeted treatment approaches as a new treatment paradigm. This study will evaluate the activity of a novel triplet combination of obinutuzumab or rituximab plus atezolizumab, and polatuzumab vedotin.

1.5.1 Rationale for Protocol BO29561, Version 7

On 1 March 2018, the Sponsor communicated in a Dear Investigator Letter the decision to stop enrollment and to discontinue atezolizumab treatment in all patients still receiving study treatment, due to a safety signal observed in Study BO29561.

The safety signal observed was the concomitant occurrence of severe and difficult-to-treat dermatitis, oral mucositis, and ocular events, refractory to standard treatment with corticosteroids, in 2 patients with relapsed/refractory (RR) FL treated with obinutuzumab (G), atezolizumab (Atezo), and polatuzumab vedotin (Pola).

This constellation of concurrent severe events is not consistent with the safety profile of the individual study drugs, neither with safety observations from ongoing studies with atezolizumab + obinutuzumab nor from studies with obinutuzumab/rituximab + polatuzumab vedotin. Hence, this unique T-cell, immune-mediated toxicity was assessed as specifically related to the triplet combination of atezolizumab + polatuzumab vedotin + obinutuzumab. Atezolizumab was discontinued in all patients still receiving study treatment due to the perceived contribution to the clinical findings, through its mode of action.

A review of the overall safety data in patients with RR DLBCL treated with atezolizumab + rituximab + polatuzumab vedotin did not reveal any new safety signals, and no immune-mediated adverse events were reported. However, based on the available preliminary safety and efficacy data both in the RR FL and RR DLBCL cohorts, the Sponsor assesses the benefit-risk of atezolizumab + obinutuzumab + polatuzumab vedotin in patients with RR FL and of atezolizumab + rituximab + polatuzumab vedotin in patients with RR DLBCL to be uncompelling.

The benefit-risk of obinutuzumab + polatuzumab vedotin and rituximab + polatuzumab vedotin combinations, without atezolizumab, remains unchanged, with no new safety signals derived from ongoing studies (see Section 1.5.4.3 and the Polatuzumab Investigator's Brochure).

1.5.2 PD-L1/PD-1 Pathway in Lymphoma

The PD-L1/PD-1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation such as chronic infection or cancer. A PD-L1 is an extracellular protein that downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Antibody-mediated PD-1 blockage has already been successfully exploited as a therapeutic strategy in solid tumors (Brahmer et al. 2012; Topalian et al. 2012; Herbst et al. 2013) and is currently being evaluated in hematologic malignancies (see Section 1.5.3). Increased PD-L1 expression has been reported on tumor cells and on immune or microenvironment cells in various lymphoid malignancies. PD-L1 is highly expressed in Hodgkin's lymphomas, anaplastic large-cell lymphoma, and DLBCL, particularly the ABC or non-GCB subtypes (Andorsky et al. 2011). Sponsor internal data (unpublished) from patients with previously untreated DLBCL enrolled in Study AVF4065g showed 67.5% of patients with lymphoma that is positive for PD-L1 as assessed by immunohistochemistry (staining $\geq$5% of cells), including 23% of patients with strong PD-L1 expression (staining in $\geq$25% of cells). In FL, PD-L1 is expressed on tumor-infiltrating lymphocytes (TILs), macrophages, peripheral blood T cells, and monocytes, but not on tumor cells (Myklebust et al. 2013).

1.5.3 Clinical Experience with PD-L1/PD-1 Pathway Inhibitors in Lymphoma

Several PD-1 and PD-L1 inhibitors are currently being investigated in various lymphoma malignancies.

Pidilizumab (CT-011), a humanized IgG-1κ monoclonal antibody that targets PD-1, has been tested in Phase I and II clinical studies in hematologic malignancies. Pidilizumab administered as a single agent after autologous SCT in patients with DLBCL (Armand et al. 2013) or in combination with rituximab in patients with relapsed FL (Westin et al. 2014) was well tolerated and showed potential clinical benefit. No autoimmune- or treatment-related Grade 3 or 4 adverse events have been reported in these studies. Among patients with relapsed FL who received pidilizumab in combination with rituximab (n=32), responders have been shown to express higher levels of PD-L1 on peripheral blood T cells and monocytes at baseline relative to

non-responders. Additionally, in this study, gene expression profile (GEP) analysis performed on baseline tumor biopsy specimens from 18 patients showed a correlation between PFS and gene expression signature of activated T-cells. The GEP studies identified 41 genes more highly expressed in Teffs compared with follicular helper T cells (TFHs). Low expression of this signature suggests a lower number of Teffs and higher number of TFHs within the tumor. Consistent with the expectation that Teffs are likely to have anti-tumor effects, whereas TFHs are likely to have pro-tumor effects, a low expression of this signature is predictive of less tumor shrinkage and resulted in a shorter PFS in this study, as median PFS was 12.7 months (95% CI: 6.5, 21.6 months) for patients with low signature expression and not reached for patients with high signature expression (Westin et al. 2014).

Nivolumab (BMS-936558), a fully human IgG4 monoclonal antibody that targets PD-1, was recently evaluated in a Phase I dose-escalation study that tested doses of 1 and 3 mg/kg in patients with relapsed or refractory lymphoid malignancies. Preliminary data indicate that 1 patient experienced dose-limiting toxicities (DLTs) of Grade 3 pneumonia and pneumonitis at the 1 mg/kg dose and 1 patient experienced DLTs of Grade 3 eosinophilia and diplopia at the 3 mg/kg dose (expansion in progress at this dose; Lesokhin et al. 2014). The objective response rate (ORR) and CR rate in patients with B-cell NHL were 28% and 7%, respectively, including an ORR of 36% in patients with DLBCL and 40% in patients with FL (Armand et al. 2014; Lesokhin et al. 2014).

Atezolizumab, which is included in the treatment regimen investigated in this study, is a first-in-class PD-L1 inhibitor being tested in multiple tumor types (Section 1.3.2). Atezolizumab was safely administered to 11 patients with various hematologic malignancies (including 7 patients with lymphoma) enrolled in Study PCD4989g. Atezolizumab 1200 mg Q3W is currently being evaluated in combination with obinutuzumab in an ongoing Phase Ib study (GO29383) in patients with relapsed or refractory DLBCL or FL (Section 1.5.4.3).

1.5.4 Rationale for Treatment Combination

Previously, this study included treatment with atezolizumab, obinutuzumab or rituximab, and polatuzumab vedotin. However, following the Dear Investigator Letter issued on 1 March 2018 due to a safety signal observed in the atezolizumab + obinutuzumab + polatuzumab vedotin (G + Atezo + Pola) treatment group (see Section 1.5.1 and Section 5.1.6), the study treatment regimen has been changed. Atezolizumab has been discontinued in all patients still receiving study treatment, and thus, previously enrolled patients with RR FL will continue to receive obinutuzumab and polatuzumab vedotin, and previously enrolled patients with RR DLBCL will continue to receive rituximab and polatuzumab vedotin, as applicable.

1.5.4.1 Mechanistic Rationale

Obinutuzumab and atezolizumab, as well as rituximab and atezolizumab, have complementary mechanisms of action, acting at different steps of the anti-tumor immune

response. Both rituximab and obinutuzumab induce tumor-cell killing with subsequent release of tumor antigens for immune presentation (immunogenic cell death) and both trigger antibody-dependent cellular cytotoxicity (ADCC). Additionally, obinutuzumab was engineered to augment ADCC, resulting in enhanced binding to FcγRIIIA/B (CD16a/b). Thus, obinutuzumab has a stronger ability to enhance T-cell priming and immune-cell activation through interactions with NK cells, T cells, dendritic cells, monocytes/macrophages, and neutrophils carrying FcγRIIIA or FcγRIIIB. Atezolizumab affects primarily the effector phase of the immune response by restoring cytotoxic T-cell function. Polatuzumab vedotin has a targeted cytotoxic effect on B cells, minimizing cytotoxic effects on hematologic cells that do not express CD79b therefore preserving T-cell function (Dornan et al. 2009; Polson et al. 2009). The combination of obinutuzumab or rituximab plus atezolizumab, and polatuzumab vedotin may provide increased clinical benefit through enhanced immunomodulatory effects combined with the cytotoxic potential of a targeted immunochemotherapy.

1.5.4.2 Nonclinical Data

Obinutuzumab or Rituximab and Atezolizumab

As presented in Section 1.2.1, nonclinical xenograft experiments consistently demonstrated superiority of obinutuzumab over rituximab.

Studies of obinutuzumab + atezolizumab and rituximab + atezolizumab have not been performed in nonclinical murine models because there are no suitable models for testing the combination. However, synergism was exhibited when the combination of a surrogate anti-mouse PD-L1 antibody, and an anti-mouse CD20-depleting antibody was tested using a syngeneic A20 lymphoma model in immune-competent mice. Results from this study demonstrated superior tumor-growth inhibition and extended time to progression when compared with either agent alone. Combination and single-agent treatments were well tolerated, with no significant loss of body weight in any group over the study duration. Enhanced combination efficacy was also observed in a study using A20 cells transfected with human CD20 and green fluorescent protein (data available upon request).

Although the anti-CD20 agent used in this study is not completely identical to obinutuzumab, the results provide compelling proof of concept for exploring this combination in clinical trials.

Obinutuzumab or Rituximab and Polatuzumab Vedotin

The anti-tumor activity of either rituximab or obinutuzumab in combination with polatuzumab vedotin was evaluated in a disseminated human MCL Z138 xenograft model in severe compromised immunodeficient (SCID) beige mice. Results from this study showed significantly increased survival with the combinations compared with each respective monotherapy (Roche Research Report 1048504).

Superiority of the combinations over rituximab or obinutuzumab alone was also demonstrated in a nonclinical study performed in an MCL Z138 xenograft model in SCID CD16 transgenic mice. This study used SCID FcgR3a transgenic mice, which express the human FcgR3a receptor on murine NK cells, allowing higher impact of NK-mediated ADCC on the efficacy measure. Both combinations showed significantly increased survival compared with each respective monotherapy (Roche Research Report 1061010).

Atezolizumab and Polatuzumab vedotin

Studies of atezolizumab + polatuzumab vedotin have not been performed in nonclinical models because there are no suitable murine models for testing the atezolizumab-based combinations. However, the complementary mechanism of action of the two drugs (Section 1.5.4.1) supports further investigation in the clinical setting.

1.5.4.3 Clinical Data

Obinutuzumab or Rituximab and Atezolizumab

No studies have been performed evaluating rituximab and atezolizumab to date.

A Phase Ib study of atezolizumab in combination with obinutuzumab in patients with relapsed or refractory FL and DLBCL (Study GO29383) is currently in progress. Preliminary results indicated that atezolizumab combined with obinutuzumab was well tolerated, with evidence of clinical activity in this patient population. A total of 49 patients were enrolled and dosed: 26 patients with FL and 23 patients with DLBCL. The doublet combination appears to be safe and tolerable, and the safety profile is consistent with what has been observed with the respective single agents and the diseases under study. As of the 14 June 2017 data cutoff, a review of safety data from Study GO29383 in patients with FL (n=26) and DLBCL (n=23) did not reveal any new safety signals. The most commonly reported (>20%) treatment-emergent adverse events included the following preferred terms: fatigue, pyrexia, nausea, diarrhea, abdominal pain, cough, and decreased appetite. The most common Grade 3–4 treatment-related adverse events were neutropenia (8%), diarrhea (8%), and pain (8%). There were no adverse events with fatal outcomes reported in patients with FL. Atezolizumab + obinutuzumab demonstrated encouraging signs of response in patients heavily pretreated and refractory with relapsed/refractory FL. The ORR at the end of induction assessment (Lugano 2014 Response Criteria by positron emission tomography and computed tomography [PET-CT]) was 56.5% in the RR FL cohort and 16% in the RR DLBCL cohort. The median duration of response and median PFS at the time of clinical cutoff in the RR FL cohort were 15.0 and 15.1 months, respectively (Palomba et al. 2017).

Rituximab and Polatuzumab Vedotin

Phase Ib/II data suggest that polatuzumab vedotin in combination with rituximab has activity in relapsed or refractory FL and DLBCL, with a generally acceptable safety and tolerability profile. As presented in Section 1.4.2.1 , the overall safety profile of polatuzumab vedotin in combination with rituximab was similar to that of single-agent polatuzumab vedotin.

In Study DCS4968g evaluating rituximab in combination with polatuzumab vedotin at a dose of 2.4 mg/kg, objective responses were observed in 7 of 9 patients with indolent B-cell lymphoma, DLBCL, or MCL (78%); 2 of the 7 patients had CRs. Median duration of response among these patients was 12.3 months (95% CI: 4.3, not estimable [NE]). Median PFS was 12.5 months (95% CI: 6.9, 17.4 months). In Study GO27834, at a dose of 2.4 mg/kg, objective responses were observed in 14 of 20 patients with FL (70%) and 21 of 39 patients with DLBCL (54%); at a dose of 1.8 mg/kg, objective responses were observed in 15 of 20 patients with FL (75%). Median duration of response was 12.9 months (95% CI: 6.7, NE) and 13.2 months (95% CI: 7.2, 21.2) for patients who received polatuzumab vedotin 1.8 mg/kg (FL) or 2.4 mg/kg (FL or DLBCL), respectively. At the 2.4 mg/kg dose, median PFS was 15.1 months (95% CI: 11.8, NE) among the 20 patients with FL and 5.6 months (95% CI: 4.2, 12.7 months) among the 39 patients with DLBCL. Among the 20 patients with relapsed or refractory FL treated with 1.8 mg/kg polatuzumab vedotin in combination with rituximab median PFS was 18.1 months (95% CI: 9.9, NE).

Preliminary data are available for two other ongoing Phase Ib/II studies: one study (GO29365) of rituximab + polatuzumab vedotin (1.8 mg/kg) + bendamustine in patients with relapsed or refractory FL or DLBCL and one study (GO29044) of rituximab + polatuzumab vedotin (1.4 or 1.8 mg/kg) + CHP in patients with relapsed or refractory B-cell lymphoma or previously untreated DLBCL.

In Study GO29365, as of 28 January 2016, safety data were available from 21 patients enrolled in the Phase Ib safety run-in or Phase II portions of the study, who received polatuzumab vedotin (1.8 mg/kg) in combination with bendamustine + rituximab. In the 1.8 mg/kg PoV + BR group, 11 of 21 patients (52%) experienced Grade 3–4 events, most common being neutropenia. The SAEs have been reported in 7 of 21 patients (33%). No Grade 5 adverse events have been reported. One patient discontinued treatment due to an adverse event. Peripheral neuropathy has been reported in 4 of 21 patients (19%). In patients with DLBCL, the only Grade 3–4 adverse event reported in 2 or more patients was lymphocyte count decreased (2 patients) while in patients with FL, Grade 3–4 adverse events reported in 2 or more patients were neutropenia (2 patients) and diarrhea (2 patients). In the efficacy evaluable population, objective responses were observed in 7 of 7 patients with FL (100%) and 3 of 7 patients with DLBCL (43%).

In Study GO29044, as of 5 February 2016, data are available from 13 patients with relapsed or refractory NHL enrolled in dose-escalation cohorts 1.0 mg/kg (n = 3),

1.4 mg/kg (n = 3), and 1.8 mg/kg (n = 7) and from 26 patients enrolled in the dose-expansion phase of the study who received polatuzumab vedotin (1.8 mg/kg) in combination with R-CHP who received polatuzumab vedotin in combination with R-CHP. In the 1.8 mg/kg PoV + R-CHP group, 15 of 32 of patients (47%) experienced Grade 3–4 events, most common being neutropenia. The SAEs have been reported in 11 of 32 patients (34%). No Grade 5 adverse events have been reported. Two patients discontinued treatment because of adverse events. Peripheral neuropathy has been reported in 9 of 32 patients (28%). Across all the three dose cohorts, the most frequently reported Grade 3–4 adverse events were neutropenia (23%), febrile neutropenia (13%), thrombocytopenia (5%), pneumonia (5%), and hypertension (5%). In the efficacy evaluable population, objective responses were observed in 29 of 31 patients (94%).

Obinutuzumab and Polatuzumab Vedotin

Several ongoing Phase Ib/II studies are assessing the safety and clinical activity of obinutuzumab + polatuzumab vedotin with or without chemotherapy.

Preliminary safety data are available from an ongoing Phase II study (GO27834) of obinutuzumab in combination with polatuzumab vedotin (1.8 mg/kg) in patients with relapsed or refractory FL or DLBCL. As of 15 April 2016, 65 patients with either relapsed or refractory follicular lymphoma (N = 30) or relapsed or refractory diffuse-large B-cell lymphoma (N = 35) have been enrolled, 64 of whom have received at least one dose of polatuzumab vedotin (1.8 mg/kg) in combination with obinutuzumab. Of the 65 patients, 82% patients experienced at least one adverse event; 26% of patients have experienced SAEs, most common being infections; 39% of patients experienced Grade 3–4 events, most common being neutropenia. There was one Grade 5 adverse event of disease progression. Four patients discontinued treatment because of adverse events, 3 of which were unrelated adverse events. Peripheral neuropathy has been reported in 11 of 64 patients (27.5%). Adverse events occurring in ≥ 10% of patients were fatigue, diarrhea, nausea, chills, constipation, dyspnea, headache, decreased appetite, dizziness, pyrexia, asthenia, and vomiting. In the efficacy evaluable population, at a dose of 1.8 mg/kg, objective responses were observed in 8 of 12 patients with FL (67%) and 3 of 15 patients with DLBCL (20%). As of the data cutoff date, median duration of response had not been reached, and PFS data were immature, with median PFS point estimates of 8.3 and 1.9 months in patients with relapsed or refractory FL and DLBCL, respectively.

Preliminary data are also available for two of the ongoing Phase Ib/II studies: one study (GO29365) of obinutuzumab + polatuzumab vedotin (1.8 mg/kg) + bendamustine in patients with relapsed or refractory FL or DLBCL and one study (GO29044) of obinutuzumab + polatuzumab vedotin (1.4 or 1.8 mg/kg) + CHP in patients with relapsed or refractory B-cell lymphoma or previously untreated DLBCL. Refer to Polatuzumab Vedotin Investigator Brochure for preliminary safety and clinical activity from these studies.

1.5.5 Benefit-Risk Assessment

In summary, this study combines treatments with different mechanisms of action that have demonstrated clinical activity against B-cell lymphoma. Currently available data for obinutuzumab or rituximab in combination with either atezolizumab or polatuzumab vedotin support and provide the rationale for a potentially improved benefit-risk ratio in patients with FL or DLBCL and further support the clinical development of the triple combination. Overlapping toxicities are anticipated and will be closely monitored and managed in the clinical trial setting with adverse event management guidance and periodic safety data review. Additionally, drug-drug interactions (DDIs) are unlikely to occur (see Section 5.1.5).

Following the Dear Investigator Letter issued on 1 March 2018 due to a safety signal observed in the G + Atezo + Pola treatment group (see Section 1.5.1 and Section 5.1.6) and evaluation of preliminary safety and efficacy data from the two study treatment groups, the Sponsor assesses the benefit-risk of atezolizumab + obinutuzumab + polatuzumab vedotin in patients with RR FL and of atezolizumab + rituximab + polatuzumab vedotin in patients with RR DLBCL to be uncompelling (see Section 1.5.1). Due to the perceived role of atezolizumab in the T-cell mediated events, the Sponsor decided to discontinue atezolizumab in all patients still receiving study treatment, but allow patients deriving benefit to continue study treatment without atezolizumab. The benefit-risk of obinutuzumab + polatuzumab vedotin and rituximab + polatuzumab vedotin combinations, without atezolizumab, remains unchanged, with no new safety signals derived from ongoing studies (see Section 1.5.4.3 and the Polatuzumab Investigator's Brochure).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of induction treatment consisting of obinutuzumab in combination with atezolizumab plus polatuzumab vedotin (G + Atezo + Pola) in patients with relapsed or refractory FL and rituximab in combination with atezolizumab + polatuzumab vedotin (R + Atezo + Pola) in patients with relapsed or refractory DLBCL, followed by post-induction treatment with G + Atezo (referred to as maintenance) in patients with FL who achieve a CR, a PR, or stable disease at EOI and post-induction treatment with R + Atezo (referred to as consolidation) in patients with DLBCL who achieve a CR or PR at EOI (see Section 3.1 for details). Specific objectives and corresponding endpoints for the study are outlined below, in accordance to study changes from Protocol BO29561, Version 7.

In this study, "study treatment" refers to the combination of all study treatment components.

2.1 SAFETY OBJECTIVE

The safety objectives for this study are as follows:

- To determine the recommended Phase II dose (RP2D) for polatuzumab vedotin when given in combination with fixed doses of obinutuzumab and atezolizumab on the basis of the following endpoint:

Incidence of DLTs during Cycles 1 and 2 of study treatment:

- To evaluate the safety and tolerability of the G + Atezo + Pola treatment group and the R + Atezo + Pola treatment group on the basis of the following endpoints:

  Nature, frequency, severity, and timing of adverse events

  Changes in clinical laboratory results during and following study treatment administration

2.2 EFFICACY OBJECTIVES

Response will be determined through use of the PET-CT scans or CT scans alone, using Revised Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014; see Appendix 5), hereinafter referred to as modified Lugano 2014 criteria. Response will be determined by the investigator.

2.2.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of induction treatment with G + Atezo + Pola in relapsed or refractory FL and R + Atezo + Pola in relapsed or refractory DLBCL on the basis of the following endpoint:

- CR at EOI, as determined by the investigator on the basis of PET-CT scans

2.2.2 Secondary Efficacy Objectives

The secondary efficacy objective for this study is to evaluate the efficacy of induction treatment with G + Atezo + Pola and maintenance treatment with G + Atezo in relapsed or refractory FL and of induction treatment with R + Atezo + Pola and consolidation treatment with R + Atezo in relapsed or refractory DLBCL on the basis of the following endpoints:

- CR at EOI, as determined by the investigator on the basis of CT scans alone
- Objective response (defined as a CR or PR) at EOI, as determined by the investigator on the basis of PET-CT scans
- Objective response (defined as a CR or PR) at EOI, as determined by the investigator on the basis of CT scans alone
- Best response of CR or PR during the study, as determined by the investigator on the basis of CT scans alone

2.2.3 Exploratory Efficacy Objectives

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of G + Atezo + Pola on the basis of the following endpoints:

- For patients who have positive PET scans at EOI:

  CR at 12 months, as determined by the investigator on the basis of PET-CT scans in FL patients

- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the pharmacokinetics of obinutuzumab, rituximab, atezolizumab, and polatuzumab vedotin when given in combination, on the basis of the following endpoints:

- Observed serum obinutuzumab concentration at specified timepoints
- Observed serum rituximab concentration at specified timepoints
- Observed serum atezolizumab concentration at specified timepoints
- Observed serum and plasma concentrations of polatuzumab vedotin and relevant analytes (total antibody, acMMAE, and unconjugated MMAE) at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab, rituximab, atezolizumab, and polatuzumab vedotin on the basis of the following endpoints:

- Incidence of human anti-human antibodies (HAHAs) to obinutuzumab during the study relative to the prevalence of HAHAs at baseline
- Incidence of human anti-chimeric antibodies (HACAs) to rituximab during the study relative to the prevalence of HACAs at baseline
- Incidence of ATAs to atezolizumab during the study relative to the prevalence of ATAs at baseline
- Incidence of ATAs to polatuzumab vedotin during the study relative to the prevalence of ATAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential effects of HAHAs, HACAs or ATAs on the basis of the following endpoint:

- Correlation between HAHA, HACA or ATA status and efficacy, safety, or PK endpoints

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify non-inherited biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers),

are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity, can increase the knowledge and understanding of lymphoma biology or study treatment mechanism of action, or can contribute to improvement of diagnostic assays, on the basis of the following endpoint:

- Association between non-inherited biomarkers (listed in Section 4.5.7) and efficacy, safety, pharmacokinetic, or immunogenicity endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study

This Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study will evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of G + Atezo + Pola in patients with RR FL and R + Atezo + Pola in patients with RR DLBCL.

Following the Dear Investigator Letter issued on 1 March 2018, enrollment has been stopped and atezolizumab treatment has been discontinued in all patients still receiving study treatment. Protocol BO29561, Version 7 formalizes these changes to the study.

A study schema is provided in Figure 1.

Overall, it was planned to have 83–92 patients enrolled in this study, at approximately 20 investigative sites around the world. As of 1 March 2018, 13 patients with RR FL and 23 patients with RR DLBCL were enrolled in the study.

To characterize the PK properties of obinutuzumab, rituximab, atezolizumab, and polatuzumab vedotin as well as the immunogenicity of obinutuzumab, rituximab, atezolizumab, and polatuzumab vedotin when given in combination, blood samples will be taken at various timepoints before and during dosing (Appendix 2).

During induction treatment, all patients will have a CT scan performed at the end of Cycle 2, to confirm absence of early disease progression. Because of the potential for tumor flares with immunotherapies, which result in early apparent radiographic progression (pseudoprogression/tumor immune infiltration), including the appearance of new lesions followed by delayed response (Wolchok et al. 2009), patients whose CT scans meet criteria for disease progression at the end of Cycle 2 may continue to receive study treatment, at the discretion of the investigator and following discussion with the Medical Monitor, if at least two of the following criteria are met:

- Absence of symptoms and signs that indicate unequivocal disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) Performance Status
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

- Patients with radiographic evidence of progression at the end of Cycle 2 who continue to receive study treatment per the above criteria should have a CT scan repeated 4–8 weeks later.

3.1.2 G + Atezo + Pola Treatment Group (Patients with Follicular Lymphoma)

3.1.2.1 Dose-Escalation Phase

The purpose of the dose-escalation phase was to identify the RP2D for polatuzumab vedotin when combined with fixed doses of obinutuzumab and atezolizumab as induction treatment. A total of 9 patients with RR FL were enrolled in the dose-escalation phase (3 patients in the Pola 1.4-mg dose cohort and 6 patients in the Pola 1.8-mg dose cohort) and treated in accordance with the treatment regimens and the dose-escalation rules described in Section 3.1.2.1.2.

No DLTs were observed at either the Pola 1.4-mg or 1.8-mg Pola dose levels. Therefore, Pola 1.8 mg was selected as the RP2D, and enrollment in the expansion phase of the study proceeded.

3.1.2.1.1 Definition of Dose-Limiting Toxicity

In this study, a DLT is defined as any one of the following events occurring during Cycles 1 and 2 of treatment and assessed by the investigator as related to study treatment:

- Adverse event of any grade that leads to a delay of more than 14 days the start of the next treatment cycle
- Hematologic adverse event that meets any of the following criteria:

  Grade 3 or 4 neutropenia in the presence of sustained fever of $>38°C$ (lasting >5 days) or a documented infection

  Grade 4 neutropenia lasting >7 days

  Grade 3 or 4 thrombocytopenia that results in significant bleeding per investigator judgment

  Grade 4 thrombocytopenia lasting >7 days
- Grade 3 or 4 non-hematologic adverse event, with the following exceptions:

  Grade 3 or 4 IRRs

  Note that IRRs may occur even after a small amount of drug has been administered (i.e., IRRs are not dose dependent).

  Grade 3 diarrhea that responds to therapy within 72 hours

  Grade 3 nausea or vomiting that occurs in the absence of premedication and responds to adequate therapy within 72 hours

  Grade 3 fatigue that resolves to Grade ≤ 2 within 7 days

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

Other toxicities occurring during Cycles 1 and 2 that are considered to be clinically relevant and related to study treatment, as determined by the investigator and the Medical Monitor may also be considered DLTs.

3.1.2.1.2 Treatment Regimens and Dose-Escalation Rules

A 3+3 dose-escalation schema was used. Induction treatment was administered in 21-day cycles, as outlined in Table 1. Obinutuzumab and atezolizumab will remain at fixed doses during the dose-escalation phase. For polatuzumab vedotin, there are two possible dose levels: 1.4 or 1.8 mg/kg. If the starting dose of 1.4 mg/kg is safe and tolerable, the polatuzumab vedotin dose will be escalated to 1.8 mg/kg. Intrapatient dose escalation is not allowed.

Table 1 Induction Treatment for Dose-Escalation Phase

Cycle	G + Atezo + Pola (21-Day Cycles)
1	Obinutuzumab 1000 mg IV on Days 1, 8, and 15 Polatuzumab vedotin 1.4 mg/kg or 1.8 mg/kg IV on Day 1
2–6	Obinutuzumab 1000 mg IV on Day 1 Atezolizumab 1200 mg IV on Day 1 Polatuzumab vedotin 1.4 mg/kg or 1.8 mg/kg IV on Day 1

IV = intravenous.

Dose escalation occurred in accordance with the rules listed below:

First Dosing Group (Polatuzumab Vedotin 1.4 mg/kg)

- A minimum of 3 patients will initially be sequentially enrolled in the first dosing group (polatuzumab vedotin 1.4 mg/kg). The 3 patients will be enrolled at least 24 hours apart.
- If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the second dosing group (i.e., polatuzumab vedotin 1.8 mg/kg) may proceed.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the dosing group will be expanded to at least 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the second dosing group may proceed.
- If 2 or more of the first 3–6 DLT-evaluable patients experience a DLT, the RP2D will have been exceeded, and dose escalation will stop and study will be discontinued.

Second Dosing Group (Polatuzumab Vedotin 1.8 mg/kg)

- A minimum of 3 patients will initially be enrolled sequentially in the second dosing group (polatuzumab vedotin 1.8 mg/kg). The 3 patients will be enrolled at least 24 hours apart.
- If none or 1 of the first 3 DLT-evaluable patients experiences a DLT, the dosing group will be expanded to at least 6 patients. If there are no further DLTs, 1.8 mg/kg will be declared the RP2D for polatuzumab vedotin.

- If 2 or more of the first 3–6 DLT-evaluable patients experience a DLT, the RP2D will have been exceeded, and 1.4 mg/kg will be declared the RP2D for polatuzumab vedotin.

The highest dose at which fewer than 2 of 6 patients DLT-evaluable patients (i.e., $<33\%$) experience a DLT was declared the RP2D for polatuzumab vedotin that will be used in the expansion phase.

On the basis of a review of real-time safety data and available preliminary PK data, dose escalation may be halted or modified by the Sponsor as deemed appropriate.

Relevant demographic, adverse event, laboratory, and PK (if available) data will be reviewed prior to dose-escalation decisions, by the Medical Monitor in consultation with the Principal Investigator and participating investigators.

Although the DLT assessment window is defined as Cycles 1 and 2, cumulative toxicities occurring beyond Cycle 2 may be considered when determining the RP2D.

Patients enrolled in the dose-escalation phase that achieved a CR, a PR, or stable disease at EOI received maintenance treatment with G + Atezo.

As of 1 March 2018, patients with RR FL eligible to or already receiving maintenance treatment will continue to receive obinutuzumab maintenance treatment, as outlined in Table 2. Maintenance treatment should start 8 weeks (± 1 week) after Day 1 of Cycle 6 and will continue until disease progression or unacceptable toxicity for up to 24 months.

Table 2 Maintenance Treatment for the G+Atezo+ Pola Treatment Group

Patients	Treatment
Patients with FL	Maintenance treatment consisting of the following, administered for 24 months [a] (from Month 1–Month 24): Obinutuzumab 1000 mg IV on Day 1 of every other month (i.e., every 2 months), starting with Month 1

FL = follicular lymphoma; IV = intravenous.

[a] 1 month = 28 days.

3.1.2.2 Expansion Phase

The expansion phase was designed to further assess the safety and efficacy of the combination of atezolizumab with obinutuzumab plus polatuzumab vedotin, when given as induction treatment and atezolizumab with obinutuzumab as maintenance treatment in patients with FL.

During the expansion phase, 34–37 patients with FL (for a total of 40 patients with FL treated at the RP2D in the dose-escalation and expansion phases) were planned to be enrolled. As of 1 March 2018, patients with RR FL will continue to be treated as outlined in Table 3.

Table 3 Induction Treatment for Expansion Phase

Cycle	G + Atezo + Pola (21-Day Cycles) Treatment Group
1–6	Obinutuzumab 1000 mg IV on Days 1, 8, and 15 Polatuzumab vedotin at 1.8 mg/kg IV on Day 1

IV = intravenous.

Patients with FL who achieve a CR, a PR, or stable disease at EOI will receive maintenance treatment with obinutuzumab, as outlined in Table 2. Maintenance treatment should start 8 weeks (± 1 week) after Day 1 of Cycle 6 and will continue until disease progression or unacceptable toxicity for up to 24 months. Polatuzumab vedotin will not be given as a post-induction treatment.

3.1.3 R + Atezo + Pola Treatment Group (Patients with Diffuse Large B-Cell Lymphoma)

Study enrollment took place in two phases: an initial safety run-in phase followed by an expansion phase.

A total of 7 patients with RR DLBCL were enrolled into the safety run-in phase at the Pola 1.8-mg dose level, and treated in accordance with the treatment regimens and the dose-escalation rules described in Section 3.1.3.1. No DLTs were observed, and Pola 1.8 mg was selected as the RP2D, and enrollment in the expansion phase of the study proceeded.

3.1.3.1 Treatment Regimens and Safety Run-In Rules

Patients with DLBCL enrolled in the safety run-in phase and the expansion phase were planned to receive induction treatment with R + Atezo + Pola for a total of 6 cycles. Patients achieving a CR or PR at EOI were eligible to receive consolidation treatment with R + Atezo.

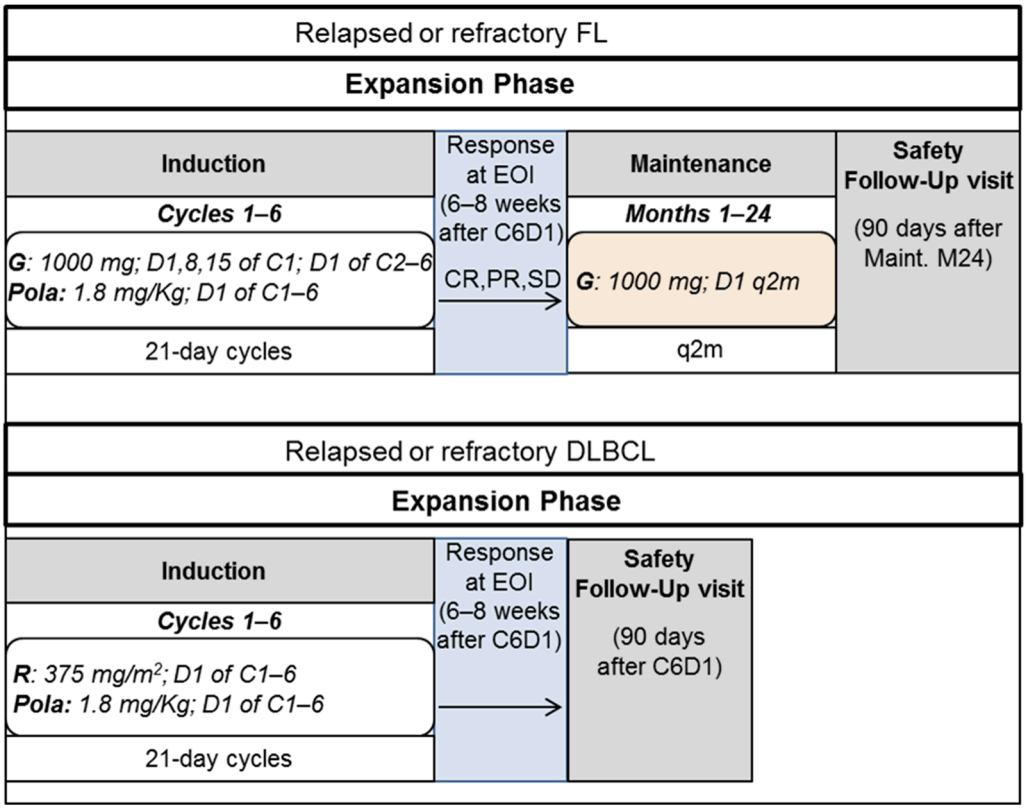
As of 1 March 2018, patients with RR DLBCL will continue to be treated as outlined in Table 4. As of Protocol BO29561, Version 7, patients who have completed or prematurely discontinued induction treatment will proceed to the safety follow-up without consolidation treatment.

Table 4 Induction Treatment for Patients with Diffuse Large B-cell Lymphoma

Cycle	R + Atezo + Pola (21-Day Cycles) Treatment Group
1–6	Rituximab 375 mg/m^2 IV on Day 1 Polatuzumab vedotin 1.8 mg/kg IV on Day 1

IV = intravenous.

Figure 1 Study Schema



C = cycle; CR = complete response; D = day; D1C6 = Day 1 of Cycle 6; EOI = end of induction; FL = follicular lymphoma; G = obinutuzumab; M = month; Pola = polatuzumab vedotin; PR = partial response; R = rituximab; q2m = every 2 months; SD = stable disease.

3.1.4 Internal Monitoring Committee

An IMC will monitor patient safety throughout the study. The IMC will include Sponsor representatives from Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis. In addition to the ongoing assessment of the incidence and nature of adverse events (particularly Grade ≥ 3 events), SAEs, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review data supporting the determination of the RP2D and then, at regular intervals during the expansion phase. At the time of each review, the IMC will make appropriate

recommendations (e.g., the study should continue as planned, additional analyses should be performed, enrollment should 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 potential new safety signals. *Following protocol amendment Version 7, patients are no longer receiving atezolizumab or polatuzumab. Therefore, regular IMC assessments will no longer take place. Ad hoc meetings to review safety data maybe called at the discretion of the Medical Monitor in case of newly identified safety signals.* Specific operational details such as the committee's composition, frequency and timing of meetings, members' roles and responsibilities, and data to be reviewed will be detailed in an IMC charter.

3.1.5 Safety Follow-Up

Patients who complete treatment or prematurely discontinue treatment will be required to perform the end-of-treatment assessments and complete the 90-day safety follow-up visit. Details are provided in the schedule of assessments (see Appendix 1 and Appendix 2).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the time when all enrolled patients with FL and all enrolled patients with DLBCL have completed the 90-day safety follow-up visit, following completion or premature discontinuation of study treatment.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

As discussed in Section 1.1, despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, FL remains essentially an incurable disease. Patients invariably relapse, and subsequent active and well-tolerated agents are needed. Although approximately 60% of patients with DLBCL have long-term responses with R-CHOP as first-line treatment, patients with advanced DLBCL have a lower chance of being cured. Success rates with salvage therapy and autologous transplantation are poor, highlighting the urgent need for novel therapeutic approaches for these patients.

On the basis of a compelling biologic and clinical rationale, as presented in Section 1.5, the combination of obinutuzumab, or rituximab with atezolizumab and polatuzumab vedotin is a promising approach to expand the number of patients with relapsed or refractory FL and DLBCL who achieve remission and to prolong response duration in these patients.

3.3.2 Rationale for Dose and Schedule

3.3.2.1 Rationale for Obinutuzumab and Rituximab Dose and Schedule

For patients with FL, the dose and schedule of obinutuzumab in the induction regimen will be 1000 mg IV on Days 1, 8, and 15 of Cycle 1 and Day 1 of each subsequent 21-day cycle (Cycles 2–6). This is based on the recommended dose and schedule of obinutuzumab in the ongoing Phase III program in patients with NHL. For this protocol, patients will be treated for 6 cycles during the induction phase. The dose and schedule of obinutuzumab in the maintenance regimen (FL) will be 1000 mg IV administered every 2 months for up to 2 years. This dosing administration is based on the obinutuzumab maintenance regimen that was administered in the Phase III GAO4753g study (Sehn et al. 2015).

For patients with DLBCL, the dose and schedule of rituximab in the induction regimen will be 375 mg/m^2 on Day 1 of each 21-day cycle (Cycles 1–6). This is based on the recommended dose and schedule for rituximab in this setting (see Rituximab Investigator's Brochure and NCCN Guidelines® 2016). For this protocol, patients will be treated for 6 cycles during the induction phase. The dose and schedule of rituximab in the consolidation regimen (DLBCL) was 375 mg/m^2 IV administered every 2 months for up to 8 months. The consolidation regimen was modeled after the FL maintenance therapy. The rationale for treatment duration is presented in Section 3.3.2.4.

3.3.2.2 Rationale for Atezolizumab Dose and Schedule

Previously, atezolizumab was administered at a flat dose consisting of one of the following: 1) 1200 mg Q3W (on Day 1 of Cycles 2–6, given in 21-day cycles with G + Pola or R + Pola as induction treatment) or 2) 1680 mg every 4 weeks (Q4W) (840 mg on Days 1 and 2 of each month, given with obinutuzumab/rituximab as post-induction treatment). Both dosages are equivalent to an average body weight–based dose of 15 mg/kg Q3W.

The dosage of 15 mg/kg Q3W was selected as the RP2D for atezolizumab on the basis of both nonclinical studies and available clinical data from Study PCD4989g, as described below.

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including the following: a) 95% tumor-receptor saturation is needed for efficacy and b) the tumor interstitial concentration-to-plasma ratio is 0.30 on the basis of tissue distribution data in tumor-bearing mice.

In Study PCD4989g, the first in-human study in patients with advanced solid tumors and hematologic malignancies, 30 patients were treated with atezolizumab at doses ranging

from 0.01–20 mg/kg Q3W during the dose-escalation stage and 247 patients were treated with atezolizumab at doses of 10, 15, or 20 mg/kg Q3W during the dose-expansion stage. Anti-tumor activity has been observed across all dose cohorts. There was no evidence of dose-dependent toxicity in this study. The maximum tolerated dose of atezolizumab was not reached, and no DLTs were observed at any dose. ATAs to atezolizumab were associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg), but patients treated at 10, 15, and 20 mg/kg maintained the expected target trough levels of drug despite the detection of ATAs. To date, no relationship has been observed between the development of measurable ATAs and safety or efficacy. After review of available PK and ATA data for a range of doses, 15 mg/kg Q3W was identified as the an atezolizumab dosing regimen that would maintain C_{trough} at ≥ 6 μg/mL, while further safeguarding against interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight–adjusted dose.

On the basis of this analysis, a fixed dose of 1200 mg Q3W (equivalent to a weight-based dose of 15 mg/kg Q3W) was defined as the RP2D.

For the Q4W dosing interval, the fixed dose of 1680 mg Q4W is the equivalent of a weight-based dose of 15 mg/kg Q3W. Population PK modeling suggests that the AUC would be comparable to that of 1200 mg Q3W (data available on request). The total dose of 1680 mg will be administered as 840 mg on Day 1 and Day 2 of each month. With the current atezolizumab manufacturing process, there is a theoretical risk of exceeding safe limits for manufacturing process-derived impurities, such as host cell DNA and endotoxins, at daily doses of >1200 mg. Thus, the total dose of 1680 mg will be split into two daily doses of 840 mg each. The manufacturing processes for atezolizumab are capable of clearing such impurities to safe levels, and tests for impurities are performed as a part of the manufacturing processes. However, splitting of the atezolizumab dose is being implemented at this stage of clinical development to further minimize the potential risk.

In Study PCD4989g, atezolizumab was safely administered to 11 patients with various hematologic malignancies (including 7 patients with lymphoma) at doses of 15 mg/kg Q3W ($n=1$) or 20 mg/kg Q3W ($n=10$). Atezolizumab 1200 mg Q3W is currently being evaluated in combination with obinutuzumab in an ongoing Phase Ib study (Study GO29383) in patients with relapsed or refractory DLBCL or FL (see Section 1.3.2). Atezolizumab was added to obinutuzumab/rituximab starting with Cycle 2 to avoid overlapping IRRs during the first infusion of obinutuzumab, which is known to be associated with the highest incidence and risk of severe IRRs. Consistent with the dosing schedule used in Study GO29383, in this study, atezolizumab was added to G/R+Pola starting with Cycle 2.

As of Protocol BO29561, Version 7, dosing with atezolizumab is discontinued in all patients still receiving study treatment.

3.3.2.3 Rationale for Polatuzumab Vedotin Dose and Schedule

For this study, the starting dose of polatuzumab vedotin will be 1.4 mg/kg, every 21 days and the dose will be escalated to a final dose of 1.8 mg/kg in relapsed or refractory FL, if tolerated. The starting dose of polatuzumab vedotin will be 1.8 mg/kg, every 21 days in relapsed or refractory DLBCL patients.

Polatuzumab vedotin dosing for this study is based on the experience from the Phase I study (DCS4968g) with single−agent polatuzumab vedotin and the Phase II study (GO27834) with polatuzumab vedotin in combination with rituximab in patients with relapsed or refractory NHL, the majority of whom had relapsed or refractory FL or DLBCL. In these studies, most evidence of anti-tumor activity was observed at doses $\geq$ 1.8 mg/kg.

Evidence from Study DCS4968g indicates that duration of study treatment might be limited by tolerability to polatuzumab vedotin at the 2.4 mg/kg dose due to high rates of treatment discontinuation due to peripheral neuropathy (sensory and/or motor) which has been identified as a known risk (see Section 5.1.4.1). Polatuzumab vedotin was shown to demonstrate single-agent activity at the 1.8 mg/kg dose level (Palanca-Wessels et al. 2015). Consequently, Study GO27834 was amended to add a cohort with the purpose of determining whether polatuzumab vedotin 1.8 mg/kg in combination with the standard dose of rituximab would result in improved tolerability while maintaining efficacy in patients with FL. Results from an ad hoc analysis comparing the 2.4 mg/kg and 1.8 mg/kg polatuzumab vedotin doses in combination with rituximab were reported (Advani et al. 2015). A high ORR was observed at both doses (76% at 2.4 mg/kg and 75% at 1.8 mg/kg), with a higher rate of CRs at 2.4 mg/kg (44% at 2.4 mg/kg and 10% at 1.8 mg/kg), although there was no observed differences in duration of response or progression free survival. At both doses, adverse event and discontinuation rates were reduced through 8 cycles of treatment (corresponding to approximately 6 months' duration) when compared with treatment through disease progression. On the basis of these findings and to minimize the risk for development of peripheral neuropathy (sensory and/or motor), polatuzumab vedotin will be given for a maximum of 6 months, and the maximum dose of polatuzumab vedotin will be 1.8 mg/kg.

Several ongoing Phase Ib/II studies are assessing the safety and clinical activity of obinutuzumab plus polatuzumab vedotin alone or in combination with chemotherapy. In study GO27834, evaluating polatuzumab vedotin in combination with rituximab/obinutuzumab, the dose of polatuzumab vedotin is 1.8 mg/kg every 21 days (see Section 1.5.4.3).

In Study GO29044 evaluating polatuzumab vedotin in combination with rituximab/ obinutuzumab-CHP, the starting dose of polatuzumab vedotin of 1.4 mg/kg and the

1.8 mg/kg dose were shown to be safe (see Section 1.5.4.3). In Study GO29365 evaluating polatuzumab vedotin in combination with obinutuzumab/rituximab–bendamustine, the dose of polatuzumab vedotin is 1.8 mg/kg. Based on the available experience with polatuzumab vedotin in combination with obinutuzumab with or without chemotherapy described above, the dose of 1.4 mg/kg is anticipated to be tolerated when polatuzumab vedotin is combined with obinutuzumab and atezolizumab. Therefore 1.4 mg/kg of polatuzumab will be the starting dose in relapsed or refractory FL patients, if tolerated, will be escalated to a final dose of 1.8 mg/kg.

Based on the available data for polatuzumab vedotin 1.8 mg/kg in combination with rituximab and chemotherapy, it is not deemed necessary to run a specific dose-escalation for polatuzumab vedotin in this treatment combination. A safety run-in is included to assess the preliminary safety of R+Pola when added to atezolizumab, before the expansion phase.

Given the maximum 6-month duration for polatuzumab vedotin owing to the risk of peripheral neuropathy with cumulative dosing, polatuzumab vedotin will not be administered as post-induction treatment.

3.3.2.4 Rationale for Treatment Duration

Previously in this study, patients with RR FL received 6 cycles of G+Atezo+Pola induction treatment followed by extended maintenance treatment with G+Atezo and patients with RR DLBCL received 6 cycles of R+Atezo+Pola induction treatment followed by extended consolidation treatment with R+Atezo.

The objective of post-induction treatment is to improve the response to induction therapy, either by improving the quality of the clinical response (e.g., converting a PR to a CR) or by eradicating minimal residual disease (MRD) to achieve a molecular response, thus reducing the risk of relapse.

Despite recent improvements in therapy for FL, including demonstrated benefit from 2-year rituximab maintenance in patients responding to first-line immunochemotherapy (Study MO18264), FL is still not considered curable, with a 6-year PFS of 59.2% (Salles et al. 2013). A Phase III study, Study GAO4753g, investigated obinutuzumab plus bendamustine (GB) compared with bendamustine alone in patients with rituximab-refractory indolent NHL ($n=396$; including 321 patients with FL). Patients in the GB group who had not experienced disease progression at EOI received obinutuzumab monotherapy every 2 months for up to 2 years. On the basis of positive results from this study, demonstrating significant improvement in PFS in the GB arm, with a median investigator-assessed PFS of 29 versus 14 months (HR=0.52; 95% CI: 0.39, 0.70; $p>0.0001$) (Sehn et al. 2015), the Independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor. These data support further investigation of obinutuzumab in combination with new targeted drugs in the setting of induction and maintenance treatment for patients with FL. On the basis of the

nonclinical rationale (presented in Section 1.5.4.2), it is hypothesized that the addition of atezolizumab to obinutuzumab may enhance and prolong the anti-tumor immune response and provide significant clinical benefit to patients. Nonclinical data demonstrating synergism between obinutuzumab and atezolizumab, associated with a low risk of overlapping toxicities, provide the rationale for administering atezolizumab as maintenance treatment on a monthly basis for the same period of 2 years. As of Protocol BO29561, Version 7, atezolizumab treatment is discontinued, and maintenance treatment will consist of obinutuzumab monotherapy (see Section 3).

Patients with relapsed or refractory DLBCL who are not suitable for or do not benefit from consolidative autologous transplantation exhibit a poor prognosis. Responses obtained with different rituximab treatment regimens tested in clinical trials (e.g., rituximab in combination with bendamustine, with gemcitabine plus oxaliplatin, or with lenalidomide) are of short duration, with the longest reported median PFS of approximately 7 months observed in one study of rituximab plus bendamustine (Ohmachi et al. 2013). Thus, 8 months of consolidation treatment with R+Atezo, for total treatment duration of approximately 12 months, aimed at prolonging the anti-tumor immune response, and was considered to be a reasonable exploratory therapeutic approach with an anticipated positive benefit-risk ratio. On the basis of the complementary mechanism of action between rituximab and atezolizumab, and considering the aggressiveness of refractory or relapsed DLBCL, the study was designed to investigate the safety and efficacy of this doublet in the consolidation setting. As of Protocol BO29561, Version 7, atezolizumab treatment is discontinued, and hence, consolidation treatment is removed. Patients with RR DLBCL will be treated only through the induction phase with rituximab and polatuzumab vedotin.

3.3.3 Rationale for PET-CT-Based Complete Response as the Primary Efficacy Endpoint

In DLBCL, the prognostic value of the post-treatment fluorodeoxyglucose (FDG) PET-CT scan has been well documented (Thomas et al. 2010; Vitolo et al. 2010). PET-CT scans have been implemented in the Lugano 2014 criteria (Cheson et al. 2014) and are commonly used to assess efficacy in medical practice and clinical trials in lymphoma. More recently, the value of post-induction PET-CT status has been investigated as a prognostic marker for long-term outcome in patients with FL. In the first-line setting, results from a pooled analysis of 246 patients enrolled in three studies and having PET-CT scans available at the end of chemoimmunotherapy showed, with a median follow-up of 55 months, a 4-year PFS in PET-CT–positive and PET-CT–negative patients of 23.2% (95% CI: 11.1%, 37.9%) versus 63.4% (95% CI: 55.9%, 70.0%; $p<0.001$), respectively, and a 4-year survival of 87.2% (95% CI: 71.9%, 94.5%) versus 97.1% (95% CI: 93.2%, 98.8%; ($p<0.0001$), respectively (Trotman et al. 2014). In the relapsed FL setting, results from a preliminary analysis of Phase II study (BO21003) comparing obinutuzumab versus rituximab monotherapy demonstrated that the post-induction PET-CT status is strongly prognostic of PFS. With a median follow-up of

32.1 months, the risk of disease progression was significantly reduced in PET-CT–negative compared with PET-CT–positive patients, regardless of the assessment criteria, either International Harmonization Project criteria (HR: 0.25; 95% CI: 0.191, 0.807; p = 0.0083) or European Organization for Research and Treatment of Cancer (EORTC) criteria (HR, 0.39; 95% CI: 0.191, 0.807; p = 0.0083) (Kostakoglu et al. 2014).

In response to developments involving PET-CT status, the 11th International Conference of Malignant Lymphoma imaging group provided an updated guidance for the use of PET-CT scan results for lymphoma staging and response assessment (Lugano 2014 criteria [Appendix 5]; Cheson et al. 2014).

3.3.4 Rationale for Biomarker Assessments

3.3.4.1 Rationale for Analysis of DLBCL Subtype, *BCL2*, and *MYC*

The DLBCL cell-of-origin prognostic subgroups (ABC and GCB), defined using gene expression profiling, have been associated with different clinical outcomes in patients receiving R-CHOP for DLBCL, with GCB subgroups demonstrating a better prognosis than ABC groups (3-year survival rate of 84% vs. 56%, respectively; p < 0.001) (Lenz et al. 2008).

A Bcl-2 overexpression has been shown to have prognostic value in DLBCL (Iqbal et al. 2006). Next-generation sequencing studies have also shown that *BCL2* is the most mutated gene in patients with GCB DLBCL, observed in up to 35% of cases (Schuetz et al. 2012). Approximately 9%–17% of patients with newly diagnosed DLBCL harbor an underlying *MYC* rearrangement, and these patients are at high risk of treatment failure with R-CHOP (Savage et al. 2009). A subset of patients with *MYC*-positive DLBCL also harbors an additional *BCL2* rearrangement. These "double-hit" lymphomas are associated with a very poor outcome (Savage et al. 2009; Dunleavy et al. 2014). Overexpression of Bcl-2 and Myc in DLBCL has also been observed in the absence of translocation. This "double-positive" DLBCL status is also associated with worse prognosis (Green et al. 2012; Johnson et al. 2012; Hu et al. 2013).

Correlative investigations are essential to understand mechanisms of both sensitivity and resistance to therapy in patients with mutational profiles that predict poor response to standard treatment.

3.3.4.2 Rationale for Assessment of Immune-Related Biomarkers

Over the last decade, tumor microenvironment and host immunity have emerged as critical determinants of cancer development and response to therapy. There is an increasing body of evidence regarding the prognostic value of TILs in B-cell lymphoma. CD8-positive cytotoxic T-cell infiltrate has been identified as a biomarker of poor prognosis in DLBCL (Galand et al. 2012). More recently, analysis of peripheral T-cell receptor repertoire demonstrated impaired T-cell diversity in B-cell lymphoma, with expansion of oligoclonal clusters of CD8-positive T cells and expansion of T-regulatory

cells associated with an increased degree of skewing observed within the CDR3 region (Fozza et al. 2014). A recent study of 12 melanoma patients treated with ipilimumab, a blocker of the immunologic checkpoint CTLA-4, showed a correlation between T-cell receptor diversity in the peripheral blood at baseline and patient outcomes (Postow et al. 2014).

This study will investigate the potential correlation of TIL signature and the status of peripheral T-cell receptor repertoire (diversity and quantity of receptors) with response to study treatment.

A fresh biopsy prior to commencing Cycle 2 is requested if an adequate accessible tumor site is available. The rationale is to better understand changes in immune-infiltrate and immune status, including PD-L1 expression after treatment with obinutuzumab and polatuzumab vedotin. Published results suggest that expression of PD-L1 in tumors correlates with response to anti−PD-1 therapy (Herbst et al. 2014; Powles et al. 2014). Other exploratory markers, such as potential predictive and prognostic markers that are related to response or clinical benefit of atezolizumab, tumor immunobiology, and tumor type markers, may also be analyzed.

Increase in T-cell activation biomarkers has been observed in peripheral blood following atezolizumab administration in cancer patients (Herbst et al. 2014). Cytokines that are characteristic of activated T-cells (e.g., IL-18, interferon gamma [IFN-γ]) and potential correlation with response to treatment will be assessed in this study.

A recent publication (Rossille et al. 2014) described the prognostic effect of soluble PD-L1 in DLBCL. The value of soluble PD-L1 as a biomarker in FL is unknown. Soluble PD-L1 levels at baseline will be assessed in this study to support an exploratory biomarker analysis.

3.3.4.3 Rationale for Analysis of CD79b: Assessment of Therapeutic Target Expression

CD79b is a signal-transducing subunit of the B-cell receptor that is rapidly internalized upon binding to polatuzumab (Jang et al. 2010). Nonclinical experiments have demonstrated that the activity of ADCs like polatuzumab vedotin depend on the presence of the target, internalization, and sensitivity to the payload drug (Zheng et al. 2009; Pfeifer et al. 2015). To ascertain the expression of CD79b in this study, CD79b will be assessed by IHC.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll patients with FL and DLBCL who meet the eligibility criteria presented below.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- ECOG Performance Status of 0, 1, or 2 (see Appendix 6)
- For G + Atezo + Pola treatment group: relapsed or refractory FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator
- For R + Atezo + Pola treatment group: relapsed or refractory DLBCL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody, in patients who are not eligible for second line combination (immuno-) chemotherapy and autologous stem-cell transplantation or who have failed second line combination (immuno-) chemotherapy or experienced disease progression following autologous stem-cell transplantation
- Histologically documented CD20-positive lymphoma as determined by the local laboratory
- FDG-avid lymphoma (i.e., PET-positive lymphoma)
- At least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension by CT scan or magnetic resonance imaging [MRI])
- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL

  If archival tissue is unavailable or unacceptable, a pretreatment core-needle, excisional or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

  Further details are provided in Section 4.5.6.

  If the patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, or if the available biopsy was performed more than 6 months prior to Day 1 of Cycle 1 (initiation of study treatment) for patients with DLBCL or more than 12 months prior to Day 1 of Cycle 1 for patients with FL, a core-needle biopsy is strongly recommended.
- 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 or to use single highly effective or combined contraceptive methods that result in a failure rate of < 1% per year during the treatment period for ≥ 5 months after the last dose of atezolizumab, ≥ 12 months after the last dose of rituximab, ≥ 12 months after the last dose of polatuzumab vedotin, and ≥ 18 months after the last dose of obinutuzumab.

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 three months after the last dose of obinutuzumab, rituximab, and atezolizumab, and five months after the last dose of polatuzumab vedotin 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:

- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Known CD20-negative status at relapse or progression
- Central nervous system (CNS) lymphoma or leptomeningeal infiltration
- Prior allogeneic SCT
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1
- Prior standard or investigational anti-cancer therapy as specified below:

  Fludarabine or alemtuzumab within 12 months prior to Day 1 of Cycle 1

  Radioimmunoconjugate within 12 weeks prior to Day 1 of Cycle 1

  Monoclonal antibody or ADC within 4 weeks prior to Day 1 of Cycle 1

Radiotherapy, chemotherapy, hormonal therapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1

Anti–PD-1, anti–PD-L1, anti-CTLA4, anti–CD137/41-BB agonist, or anti-CD40 agonist antibodies

- Clinically significant toxicity (other than alopecia) from prior treatment that has not resolved to Grade ≤ 2 (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0) prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medications, including, but not limited to, prednisone, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor agents within 2 weeks prior to Day 1 of Cycle 1

  Treatment with inhaled corticosteroids and mineralocorticoids is permitted.

  If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg of prednisone or equivalent can be given for a maximum of 5 days, but all tumor assessments must be completed prior to initiation of corticosteroid treatment.
- History of solid organ transplantation
- History of severe allergic or anaphylactic reaction to humanized, chimeric, or murine monoclonal antibodies
- Known hypersensitivity or allergy to murine products
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab, obinutuzumab, rituximab, or polatuzumab vedotin formulations
- Known history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis or evidence of active pneumonitis on screening chest CT scan.

  History of radiation pneumonitis in the radiation field (fibrosis) is allowed.
- Active bacterial, viral, fungal, or other infection or any major episode of infection requiring treatment with IV antibiotics within 4 weeks of Day 1 of Cycle 1

  Caution should be exercised when considering the use of obinutuzumab and rituximab in patients with a history of recurring or chronic infections.
- Receipt of oral or intravenous antibiotics for treatment of serious infections within 4 weeks prior to Day 1 of Cycle 1
- Positive for hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at screening
- Known history of HIV positive status

  For patients with unknown HIV status, HIV testing will be performed at screening if required by local regulations.
- History of PML

- Vaccination with a live virus vaccine or live attenuated vaccine within 28 days prior to Day 1 of Cycle 1, or anticipation that such a live, attenuated vaccine will be required during the study
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:

  Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer

  Any previously treated malignancy that has been in remission without treatment for ≥ 2 years prior to enrollment
- History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (Appendix 10) for a comprehensive list of autoimmune diseases)

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study.

  Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.
- Grade > 1 peripheral neuropathy present at screening
- Evidence of any significant, uncontrolled concomitant disease 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 previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm)
- Major surgical procedure other than for diagnosis within 28 days prior to Day 1 of Cycle 1, or anticipation of a major surgical procedure during the course of the study
- Inadequate hematologic function (unless due to underlying lymphoma), defined as follows:

  Hemoglobin < 9 g/dL

  ANC $< 1.5 \times 10^9$/L

  Platelet count $< 75 \times 10^9$/L
- Inadequate liver function defined as follows (unless due to underlying lymphoma):

  For patients enrolled in the dose escalation:

  AST $>$ Upper limit of normal (ULN) or serum total bilirubin $>$ ULN

For patients enrolled in the expansion:

AST or ALT $>2.5\times$ ULN

Serum total bilirubin $>1.5\times$ ULN (or $>3\times$ ULN for patients with Gilbert syndrome)

- Any of the following abnormal laboratory values (unless due to underlying lymphoma):

  Creatinine >1.5 times the ULN (unless creatinine clearance is normal) or calculated creatinine CL <40 mL/min (using the Cockcroft-Gault formula; Appendix 11)

  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

- Pregnant or lactating, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to Day 1 of Cycle 1.

- Life expectancy <3 months
- Unable to comply with the study protocol, in the investigator's judgment

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study of G + Atezo + Pola in patients with relapsed or refractory FL and R + Atezo + Pola in patients with relapsed or refractory DLBCL. During the dose-escalation phase, an interactive voice or web-based response system (IxRS) was used to assign patients with relapsed or refractory FL to dosing groups that vary according to the dose of polatuzumab vedotin given during induction treatment. During the expansion phase, patients with relapsed or refractory FL and DLBCL will receive polatuzumab vedotin at the RP2D during induction treatment. Atezolizumab and obinutuzumab or rituximab was to be given at stable doses to all patients, during both induction and post-induction treatment. Post-induction treatment (for eligible patients only) will depend on lymphoma histology (see Section 3.1 for details). As of 1 March 2018, patients with RR FL in the expansion phase will continue to be treated with G+Pola during induction (see Table 3) and patients on maintenance treatment will continue treatment with obinutuzumab (see Table 2). Patients with RR DLBCL will continue to be treated with R + Pola during induction (see Table 4), and patients with RR DLBCL who have completed or prematurely discontinued induction treatment will proceed to the safety follow-up without consolidation treatment.

Enrollment tracking will be performed through use of the IxRS. Prior to initiation of screening, the study site should confirm via the IxRS that slots are available for enrollment. 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 enrolled via the IxRS. The Sponsor will communicate to the sites impending closure of screening for the dose-escalation and expansion phases.

4.3 STUDY TREATMENT

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

As of Protocol BO29561, Version 7, dosing with atezolizumab is discontinued in all patients.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Obinutuzumab

Obinutuzumab will be supplied by the Sponsor as an IMP. Obinutuzumab will be provided as a single-dose, sterile liquid formulation in a 50-mL glass vial containing 1000 mg/40 mL of obinutuzumab. In addition to the drug substance, the liquid is also composed of histidine, trehalose, and poloxamer 188. For information on the formulation and handling of obinutuzumab, see the Obinutuzumab Investigator's Brochure and the Pharmacy Manual.

4.3.1.2 Atezolizumab

Atezolizumab was supplied by the Sponsor as an IMP. Atezolizumab Drug Product is provided in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume. Extraction of 14 mL of atezolizumab solution will contain an 840-mg dose. For information on the formulation and handling of atezolizumab, see the Atezolizumab Investigator's Brochure and the Pharmacy Manual.

4.3.1.3 Polatuzumab Vedotin

Polatuzumab vedotin will be supplied by the Sponsor as an IMP. Polatuzumab vedotin will be provided as a sterile, white to off-white, preservative-free lyophilisate in single-use vials. For information on the formulation and handling of polatuzumab vedotin, see the polatuzumab vedotin Investigator's Brochure and the Pharmacy Manual.

4.3.1.4 Rituximab

Rituximab will be supplied by the Sponsor as an IMP. Rituximab is packaged in 10 mL (100-mg) and 50-mL (500-mg) single-dose, pharmaceutical-grade glass vials at a concentration of 10 mg/mL of protein. The antibody is formulated for IV injection as a sterile product in a solution of sodium chloride (pH 6.5) containing polysorbate 80 and sodium citrate. For information on the formulation and handling of rituximab, see the Rituximab Investigator's Brochure and the Rituximab Pharmacy Manual.

4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized in Table 6, Table 7, and Table 8 (see Sections 4.3.2.4 and 4.3.2.5). Premedication should be administered as described in Section 4.3.2.7.

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

4.3.2.1 Obinutuzumab

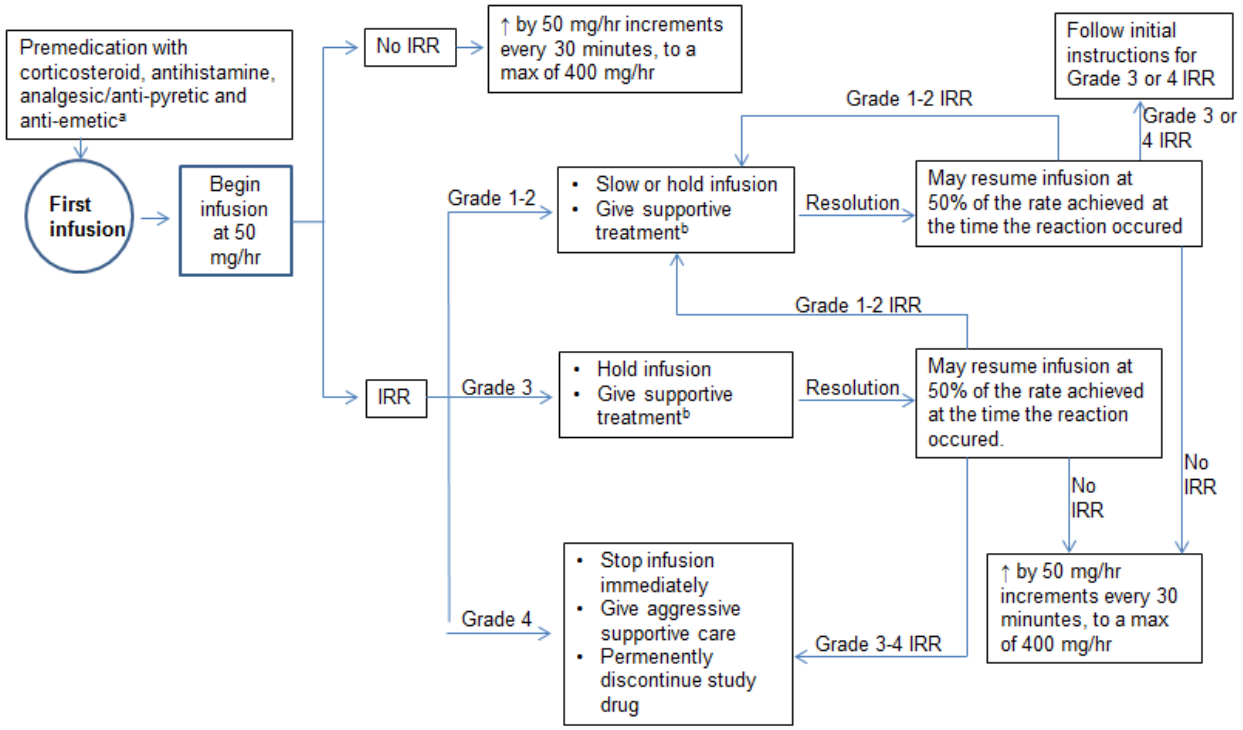
Obinutuzumab will be administered by IV infusion at an absolute (flat) dose of 1000 mg on Days 1, 8, and 15 of the first cycle and on Day 1 of each subsequent cycle during induction treatment, and on Day 1 of every other month (i.e., every 2 months) during maintenance treatment.

Obinutuzumab should be administered as an IV infusion through a dedicated line in an environment in which full resuscitation facilities are immediately available and under the close supervision of an experienced physician. Obinutuzumab infusions will be administered per the instructions outlined in Figure 2 and Figure 3. For patients with bulky lymphadenopathy, the infusion may be given slowly over a longer period of time, or the dose may be split and given over more than 1 day.

No dose modification for obinutuzumab is allowed. Additional guidelines for treatment delays or discontinuation are provided in Section 5.1.6.

Premedication with a corticosteroid, antihistamine, and analgesic/antipyretic, as outlined in Section 4.3.2.7 and Table 9, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 9.

Figure 2 Guidelines for Obinutuzumab Infusions: First Infusion

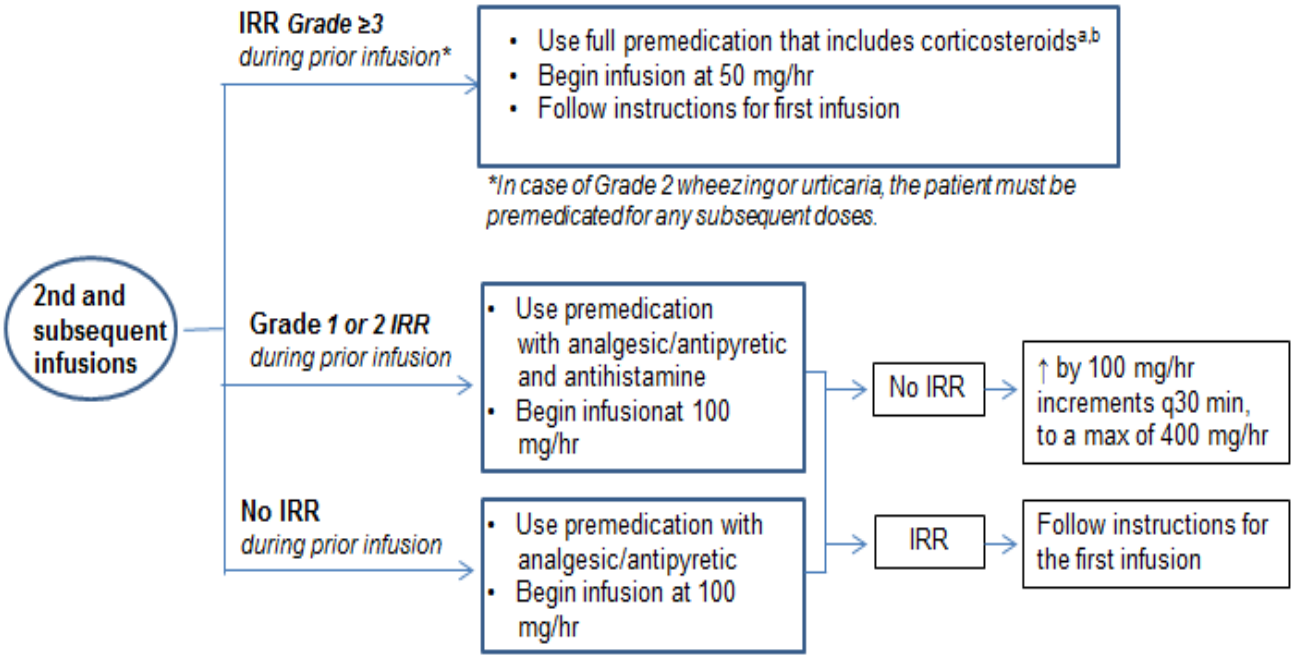


IRR = infusion-related reaction.

[a] All patients should receive full premedication with oral corticosteroid, oral analgesic/anti-pyretic, and antihistamine prior to the first obinutuzumab infusion. Refer to Section 4.3.2.7 for details.

[b] Supportive treatment should include acetaminophen/paracetamol and an antihistamine such as diphenhydramine, if not administered within the previous 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg oral prednisone or equivalent), and/or bronchodilators. For anaphylaxis precautions, see Appendix 9.

Figure 3 Guidelines for Obinutuzumab Infusions: Second and Subsequent Infusions



IRR = infusion-related reaction.

[a] Patients should receive full premedication with oral corticosteroid, antihistamine, and oral analgesic/anti-pyretic prior to the obinutuzumab infusion. Refer to Section 4.3.2.7 for details. In the case of a recurrent Grade 3 IRR, obinutuzumab may be discontinued at the discretion of the investigator, following an individual benefit-risk assessment.

[b] Patients who experience wheezing, urticaria, or other symptoms of anaphylaxis must receive full premedication prior to all subsequent doses.

4.3.2.2 Atezolizumab

Atezolizumab was administered by IV infusion at a flat dose consisting of one of the following: a) 1200 mg Q3W (on Day 1 of Cycles 2-6, given in 21-day cycles as induction treatment) or b) 1680 mg Q4W (840 mg on Days 1 and 2 of each month, given as maintenance or consolidation treatment). Detailed atezolizumab dosing regimens are provided in Table 6 for induction treatment and in Table 8 for post-induction treatment (Sections 4.3.2.4 and 4.3.2.5).

No dose modification for atezolizumab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.6.

4.3.2.3 Polatuzumab Vedotin

Polatuzumab vedotin will be administered by IV infusion on Day 1 of Cycles 1–6 during induction treatment; polatuzumab vedotin will not be administered during consolidation or maintenance treatment. For relapsed or refractory FL, during the dose-escalation phase, the dose of polatuzumab vedotin for each patient will depend on dose assignment (1.4 or 1.8 mg/kg). During the expansion phase, the dose of polatuzumab vedotin for each patient will depend on the RP2D established during the dose-escalation phase. For relapsed or refractory DLBCL, during the safety run-in phase the starting dose of polatuzumab vedotin will be 1.8 mg/kg. During expansion phase, the dose of polatuzumab vedotin will be 1.8 or 1.4 mg/Kg depending on the tolerability of the combination observed during Safety run-in.

The patient's weight obtained during screening (Days −28 to −1) should be used for dose determination for all treatment cycles. If the patient's weight within 96 hours prior to Day 1 of a given treatment cycle is $>10\%$ higher or lower than 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.

Polatuzumab vedotin infusions will be administered as follows:

- The initial dose will be administered to patients who are well hydrated over 90 ($\pm$10) minutes.
- The polatuzumab vedotin infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the Cycle 1 Day 1 and Cycle 2 Day 1 dose, patients will be observed for 90 minutes for IRRs. If prior infusions have been well tolerated, subsequent doses of polatuzumab vedotin may be administered over 30 ($\pm$10) minutes, followed by a 30-minute observation period after the infusion.

4.3.2.4 Rituximab

Rituximab will be administered by IV infusion at the dose of 375 mg/m^2 on Day 1 of Cycles 1−6 during induction treatment and on Day 1 of every other month (i.e., every 2 months) during consolidation treatment.

Body surface area (BSA) will be determined at screening and 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 (defined as body mass index ≥ 30 kg/m^2), there is no BSA cap and actual body weight, not adjusted weight, is recommended. Empiric dose adjustment for obese patients may be implemented per institutional guidelines.

The infusion of rituximab may be split over two days if the patient is at increased risk for an IRR (high tumor burden or 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 two days, both infusions must occur with appropriate premedication (see Section 4.3.2.7) and at the first infusion rate (see Table 5).

Rituximab infusions will be administered according to the instructions in Table 5. If a patient tolerates the first three cycles of study treatment without significant infusion reactions, rituximab may be administered as a rapid infusion in accordance with local institutional guidelines.

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

Rituximab should be administered as a slow IV infusion through a dedicated line. 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 5 Administration of First and Subsequent Infusions of Rituximab

First Infusion (Day 1 of Cycle 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 has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time when the reaction occurred).	• If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, use full premedication, including 100 mg of prednisone/prednisolone or 80 mg of methylprednisolone or equivalent (until no further IRR 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 an 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 has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time when the reaction occurred).

No dose modification for rituximab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.6.

Premedication with a corticosteroid, analgesic/antipyretic, and antihistamine, as outlined in Section 4.3.2.7, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 9.

4.3.2.5 Induction Treatment with Obinutuzumab or Rituximab, and Polatuzumab Vedotin (G+Pola or R+Pola)

Patients will receive induction treatment, administered in 21-day cycles, as follows:

- Patients with FL will receive 6 cycles of induction treatment consisting of obinutuzumab and polatuzumab vedotin for Cycles 1–6 as outlined in Table 6.
- Patients with DLBCL will receive 6 cycles of induction treatment consisting of rituximab and polatuzumab vedotin for Cycles 1–6 as outlined in Table 7.

Obinutuzumab or rituximab will be administered first, followed by a line flush (unless there is a central line with more than one line/port) and then polatuzumab vedotin.

For patients at increased risk for IRRs (high tumor burden), the first obinutuzumab and rituximab infusion may be split and administered over 2 days. If split, obinutuzumab should be given as 100 mg on Day 1 and 900 mg on Day 2.

For patients who experience an IRR during obinutuzumab or rituximab infusion, administration of polatuzumab vedotin may be delayed by 1 day if clinically required.

Table 6 Induction Treatment in Patients with Follicular Lymphoma

Treatment	Dose	Route	Regimen (21-day Cycles)	
			Cycle 1	Cycle 2–6
Obinutuzumab	1000 mg	IV	Days 1, 8, and 15	Day 1
Polatuzumab vedotin	1.4 mg/kg or 1.8 mg/kg	IV	Day 1	Day 1

FL = follicular lymphoma; IV = intravenous.

Table 7 Induction Treatment in Patients with Diffuse Large B-cell Lymphoma

Treatment	Dose	Route	Regimen (21-Day Cycles)	
			Cycle 1	Cycles 2–6
Rituximab	375 mg/m^2	IV	Day 1	Day 1
Polatuzumab vedotin	1.8 mg/kg [a]	IV	Day 1	Day 1

DLBCL = diffuse large B-cell lymphoma; IV = intravenous.

[a] Dose may be de-escalated to 1.4 mg/kg.

4.3.2.6 Post-Induction Treatment

Patients with FL who achieve a CR, a PR, or stable disease at EOI will receive maintenance treatment with obinutuzumab for 24 months, as outlined in Table 8.

Maintenance treatment should start 8 weeks (±1 week) after Day 1 of Cycle 6 and will continue until disease progression or unacceptable toxicity for up to 24 months.

Table 8 Maintenance Treatment for Patients with Follicular Lymphoma

Treatment	Dose	Route	Regimen (Months 1–24)
Obinutuzumab	1000 mg	IV	Day 1 of every other month (i.e., every 2 months), starting with Month 1

FL = follicular lymphoma; IV = intravenous.

4.3.2.7 Premedication and Other Prophylaxis Treatment

Patients should receive premedication as outlined in Table 9 below.

Table 9 Premedication

Timepoint	Patients Requiring Premedication	Premedication	Administration
Cycle 1, Day 1	• All patients	• Oral corticosteroid [a]	Administer at least 1 hour prior to obinutuzumab or rituximab infusion
	• All patients	• Antihistamine drug [b] • Oral analgesic/anti-pyretic [c]	Administer at least 30 minutes prior to obinutuzumab or rituximab infusion
	• Patients at risk for TLS (e.g., because of bulky disease or renal impairment (creatinine clearance $<$70 mL/min)	• Allopurinol or suitable alternative such as rasburicase, along with adequate hydration	Administer prior to obinutuzumab or rituximab infusion
Cycle 1, Days 8 and 15 Cycles 2 and beyond, Day 1	• Patients with no IRR during the previous infusion	• Oral analgesic/anti-pyretic [c]	Administer at least 30 minutes prior to obinutuzumab infusion. For patients receiving rituximab premedication may be omitted at the investigator's discretion.
	• Patients with Grade 1 or 2 IRR during the previous infusion	• Antihistamine drug [b] • Oral analgesic/anti-pyretic [c]	Administer at least 30 minutes prior to obinutuzumab infusion
	• Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion • Patients with bulky disease	• Oral corticosteroid [a]	Administer at least 1 hour prior to obinutuzumab or rituximab infusion
		• Antihistamine drug [b] • Oral analgesic/anti-pyretic [c]	Administer at least 30 minutes prior to obinutuzumab infusion
	• Patients still at risk for TLS	• Allopurinol or suitable alternative such as rasburicase, along with adequate hydration	Administer prior to obinutuzumab or rituximab infusion

IRR = infusion-related reaction; TLS = tumor lysis syndrome.

[a] Treat with 100 mg of prednisone or prednisolone, 20 mg of dexamethasone, or 80 mg of methylprednisolone. Hydrocortisone should not be used because it has not been effective in reducing rates of IRR.

[b] For example, 50 mg of diphenhydramine.

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

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (obinutuzumab, rituximab, and polatuzumab vedotin) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.4 Post-Trial Access to, Obinutuzumab, Rituximab, and Polatuzumab Vedotin

Patients may continue to receive study treatment and undergo scheduled assessments as part of an extension study. Currently, the Sponsor does not have any plans to provide *post-trial access to* any *IMP* or interventions to patients who *do not qualify for* the *extension study.* The Roche Global Policy on Continued Access to Investigational Medicinal Product *is* available at the following Web site:

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

4.4 CONCOMITANT 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 the screening period to the visit at EOI or at the end of post-induction treatment, whichever occurs later. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Premedication should be administered as described in Section 4.3.2.7.

Patients who use oral contraceptives, hormone replacement therapy, or other maintenance therapy should continue their use.

Patients using concomitant medication that could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants) may be at a greater risk of bleeding. When possible, replace prior vitamin K antagonist therapy with low-molecular-weight heparin (LMWH) prior to Day 1 of Cycle 1.

Hematopoietic growth factors are allowed if clinically indicated and used in accordance with the prescribing information. Granulocyte colony-stimulating factor (G-CSF) may be administered in each cycle of therapy as primary prophylaxis for neutropenia, per American Society of Clinical Oncology, EORTC, and European Society for Medical Oncology guidelines or per each site's institutional standards.

Prophylactic treatment with antibiotics should be administered as per standard practice.

The patients who receive strong CYP3A4 inhibitors or P-glycoprotein (P-gp) inhibitors in combination with polatuzumab vedotin will be closely monitored for any adverse reactions.

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards.

4.4.2 Prohibited Therapy

Use of the following therapies (excluding protocol-specified treatments) is prohibited during the study:

- Any anti-cancer therapy, approved or investigational, other than intrathecal CNS prophylaxis
- Hormonal therapy other than contraceptives, stable hormone replacement therapy, or megestrol acetate
- Biologic agents other than hematopoietic growth factors (as described in Section 4.3.2.7)
- Immunostimulatory agents, including, but not limited to, IFN-α, IFN-γ, or IL-2

  Immunostimulatory agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions. Patients should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.
- Vaccines, as outlined below:

  Any live, attenuated vaccine (e.g., FluMist®) is prohibited while the patient is receiving atezolizumab and for a period of five months after discontinuation of atezolizumab. Inactivated influenza vaccines are allowed only during flu season.

  Vaccination with live vaccines is not recommended during treatment with obinutuzumab and until B-cell recovery.

4.5 STUDY ASSESSMENTS

See Appendix 1 and Appendix 2 for the schedules of assessments performed during the study.

4.5.1 Informed Consent Forms, Screening Log, and Patient Screening

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

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

Results of standard-of-care tests or examinations performed prior to obtaining informed consent, and within the defined window, may be used as screening and baseline assessments (see Appendix 1 and Appendix 2); such tests do not need to be repeated for screening purposes (e.g., screening tumor assessment).

Study treatment should be initiated within 28 days after the Informed Consent Form has been signed.

Patients who fail screening based on longer waiting time for certain results or due to study administrative reasons (e.g., a dose cohort on enrollment hold) can be rescreened at a later date, and only once, if they were deemed eligible before the screen failure. The decision to rescreen individual patients will be made jointly by the Roche Medical Monitor and the investigator and any other person the investigator or Medical Monitor considers necessary to assist with this decision. Any such decision and the reasons for it will be clearly documented. Any out of window assessments need to be repeated and undergo a complete review by the Roche Medical Monitor.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and alcohol and drug abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within seven days prior to the screening period will be recorded.

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

The following clinical parameters relative to disease history, diagnosis, and prognostic indices will be recorded at screening:

- Date of initial diagnosis
- ECOG Performance Status (see Appendix 6)
- B symptoms (unexplained fever $>38°C$, night sweats, and unexplained weight loss $>10\%$ of body weight over 6 months)

- Ann Arbor staging (see Appendix 7)
- For patients with FL: Follicular Lymphoma International Prognostic Index (FLIPI) and Follicular Lymphoma International Prognostic Index 2 (FLIPI2) (see Appendix 8)
- For patients with DLBCL: The IPI (see Appendix 8)
- Prior anti-lymphoma treatment, as well as response to prior treatment, date of disease progression in relation to start date of prior treatment, and date of last dose of prior treatment

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, 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, the physical examination should include evaluation for the presence of enlarged nodes, palpable hepatomegaly, and splenomegaly. This information will be recorded on the appropriate tumor assessment eCRF.

At subsequent visits (or as clinically indicated), targeted (limited, symptom-directed) physical examinations should be performed. Targeted physical examinations should be limited to systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline) (see Section 4.5.5).

Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. Vital sign measurements will be performed as outlined in the schedules of assessments (see Appendix 1 and Appendix 2), but the associated data, other than the data collected at screening, do not need to be recorded on the eCRF (except in the case of an adverse event as presented in Section 5.3.5.6).

4.5.5 Tumor and Response Evaluations

All evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of PET and CT scans using the Lugano 2014 criteria (see Appendix 5). In this study, the Lugano 2014 criteria for a PET-CT-based CR and PR have been modified, as outlined below:

- A designation of PET-CT-based CR requires normal bone marrow by morphology for patients with bone marrow involvement at baseline. If indeterminate by morphology, immunohistochemistry should be negative.
- A designation of PET-CT–based PR requires that CT-based response criteria for a CR or PR be met in addition to the PET-CT–based response criteria for a PR.

4.5.6 Radiographic Assessments

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

The CT scans with oral and IV contrast should include chest, abdomen, and pelvic scans. The CT scans of the neck should be included if clinically indicated (i.e., if evidence of disease upon physical examination) and must be repeated throughout the study if there is disease involvement at baseline.

The PET-CT scans and diagnostic CT scans should be acquired according to a standardized imaging manual, which will be provided to all sites.

If contrast is medically contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans of the chest, abdomen, and pelvis (and neck, if clinically indicated) and a non-contrast CT scan of the chest may be performed. If MRI scans cannot be obtained, CT scans without contrast are permitted as long as these allow consistent and precise measurement of the targeted lesions during the study treatment period.

The same radiographic assessment modality must be used for all response evaluations to ensure consistency across different timepoints (including unscheduled assessments).

A full tumor assessment, including radiographic assessment, must be performed any time disease progression or relapse is suspected. Additional details regarding imaging procedures will be provided in the Imaging Manual.

4.5.6.1 Bone Marrow Assessments

Bone marrow examinations are required at screening for staging purposes in all patients and should be performed within approximately 3 months prior to Day 1 of Cycle 1.

If bone marrow infiltration is present at screening, a bone marrow biopsy is required at the EOI response assessment for all patients who may have achieved a CR. In patients with a PR at EOI, a subsequent bone marrow examination may be required to confirm a CR at a later timepoint.

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

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Local Laboratory Assessments

Samples for the following laboratory tests will be analyzed at the study site's local laboratory for analysis:

- Hematology: hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum or plasma): sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase (ALP), LDH, uric acid, glycosylated hemoglobin (HbA_{1c}), amylase, and lipase.

  HbA_{1c} will be measured only at screening and can be obtained in a non-fasting state.
- Thyroid-stimulating hormone, triiodothyronine, thyroxine (T4)
- β2 microglobulin
- Coagulation: INR, aPTT (or PTT), and PT
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening (within 7 days of Day 1 of Cycle 1). In addition, urine pregnancy testing is required monthly during induction. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Viral serology

  Hepatitis B testing includes HBsAg and total HBcAb.

  Hepatitis C testing includes HCV antibody.
- Quantitative immunogloblulins: IgA, IgG, and IgM

Central Laboratory Assessments

The following samples will be sent to one or several Sponsor-designated central laboratories or to the Sponsor for analysis:

- Serum samples for obinutuzumab PK analysis using a validated assay
- Serum samples for rituximab PK analysis using a validated assay
- Serum samples for atezolizumab PK analysis using a validated assay

- Serum and plasma samples for polatuzumab vedotin PK analysis using a validated assay
- Serum samples for assessment of HAHAs to obinutuzumab using a validated assay
- Serum samples for assessment of HACAs to rituximab using a validated assay
- Serum samples for assessment of ATAs to atezolizumab using a validated assay
- Serum samples for assessment of ATAs to polatuzumab vedotin using a validated assay
- Tumor tissue samples and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL, and for exploratory research on candidate biomarkers (see Table 10).

  The specimen must contain adequate evaluable tumor cells (≥20% for excisional biopsy and ≥50% for core biopsy).

  Formalin-fixed paraffin-embedded tissue blocks are preferred over slides. Tissue blocks that are not formalin fixed will be accepted in countries that use a fixative other than paraformaldehyde, but information on the type of fixative should be included. If a tissue block is not available, 15–20 serial, freshly cut, unstained slides accompanied by a punch biopsy may be sent. A tumor block or punch biopsy is required for construction of a tissue microarray. If less than 15–20 unstained serial slides are available, the study site should consult the Sponsor (or delegate) regarding the acceptability of a fewer number of slides.

  If archival tissue is unavailable or unacceptable according to the above criteria, a pretreatment core-needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

  If the patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, or if the available biopsy was performed more than 6 months prior to Day 1 of Cycle 1 (initiation of study treatment) for patients with DLBCL or more than 12 months prior to Day 1 of Cycle 1 for patients with FL, a core-needle biopsy is strongly recommended.

  The sample should be shipped according to instructions provided in the laboratory manual. The remainder of the tissue blocks will be returned to the local pathology laboratory, according to country-specific procedures.

  Analysis methods will be detailed in the Biomarker Analysis Plan.
- Tumor biopsy samples obtained prior to the start of Cycle 2 and at the time of progression (unless no adequate tumor site is accessible) for exploratory research on candidate biomarkers (Table 10)
- Serum samples for exploratory research on candidate biomarkers (see Table 10)
- Whole blood samples for exploratory research on candidate biomarkers (see Table 10)
- Whole blood samples for isolation of peripheral blood mononuclear cells for exploratory research on candidate biomarkers (see Table 10)

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 10.

Table 10 Proposed Non-Inherited Biomarkers for Exploratory Research

Sample Type	Timing	Proposed Non-Inherited Biomarkers
Archival or fresh tumor tissue	Prior to study (archival) or baseline (fresh)	• For patients with DLBCL only: DLBCL cell-of-origin subtype (ABC vs. GCB), *MYC*, *BCL2*, Epstein-Barr virus status • CD79b • Lymphoma-related genetic changes (DNA) and gene expression (mRNA) • PD-L1, HLA-1 • CD8 and other biomarkers of T-cell subpopulations • Biomarkers of other immune cells (such as macrophages)
Tumor tissue biopsy	Prior to the start of Cycle 2 and at the time of progression (unless no adequate tumor site is accessible)	• PD-L1 • CD8 and other biomarkers of T-cell subpopulations and other immune cells
Plasma	Baseline	• Soluble PD-L1
Plasma	Baseline and subsequent timepoints during treatment	• Cytokines characteristic of T-cell activation (e.g., IL-18, IFN-γ)
PBMCs isolated from whole blood	Baseline and subsequent timepoints during treatment	• T-cell receptor repertoire
Whole blood	Baseline and subsequent timepoints during and after treatment	• Lymphocyte immunophenotyping, including B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK cell counts (CD16 and CD56)

ABC = activated B cell–like; DBLCL = diffuse large B-cell lymphoma; GCB = germinal-center B cell-like; HLA = human lymphocyte antigen; IFN-γ = interferon gamma; IL = interleukin; NK = natural killer; PBMC = peripheral blood mononuclear cell.

Note: Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in this table.

Samples collected for PK and immunogenicity analyses may be used for assay development purposes and additional safety and immunogenicity assessments, as appropriate.

Biological samples will be destroyed when the final Clinical Study Report has been completed, unless the patient gives specific consent for the leftover samples to be stored for optional exploratory research (see Section 4.5.9).

4.5.8 Electrocardiograms

Single, resting, 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedules of assessments (see Appendix 1 and Appendix 2), and may be obtained at unscheduled timepoints as clinically indicated. ECGs for each patient should be obtained using the same machine wherever possible. Interpretation of the ECG should be performed by the investigator.

4.5.9 Samples for Roche Clinical Repository

4.5.9.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (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 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. The RCR specimens will be used to achieve the following objectives:

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

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR are contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site.

4.5.9.3 Sample Collection

The following samples will be collected for research purposes, including, but not limited to, research on dynamic (non-inherited) biomarkers related to obinutuzumab, atezolizumab, polatuzumab vedotin, NHL, or other types of cancer:

- Peripheral blood (i.e., whole blood, plasma, and serum)
- Leftover tumor tissue from lymph node biopsy (archival and/or fresh biopsy)
- Leftover peripheral blood

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

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

4.5.9.4 Confidentiality

Confidentiality for All Roche Clinical Repository Specimens

Specimens and associated data will be labeled with a unique patient identification number.

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

Data 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.

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.

Additional Confidentiality for Specimens Used for Genetic Research

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens collected for genetic research. Upon receipt by the RCR, specimens for genetic research are "double-coded" by

replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

4.5.9.5 Consent to Participate in the Roche Clinical Repository

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

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

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

4.5.9.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study BO29561 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study BO29561.

4.5.9.7 Monitoring and Oversight

The RCR specimens will be tracked in a manner consistent with Good Clinical Practice (GCP) by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche's 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.

4.6 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 (e.g., consistent failure to show up for scheduled visits)

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.

If a patient withdraws consent, this request must be documented in the source documents and signed by the investigator. Study personnel may use a public information source (e.g., county records) to obtain information about survival status.

4.6.2 Study Treatment Discontinuation

Study treatment should be permanently discontinued in patients who experience any of the following:

- Anaphylaxis, acute respiratory distress, or Grade 4 IRR

  If a Grade 3 IRR is recurrent during the second and subsequent cycles, study treatment may be discontinued at the discretion of the investigator, following an individual benefit-risk assessment.
- Life-threatening adverse event
- Grade ≥ 3 non–immune-related adverse event that is considered to be related to study treatment and does not resolve to Grade ≤ 2 within 21 days
- Non–immune-related adverse event that is considered to be treatment related and requires study treatment to be withheld for > 21 days
- Grade ≥ 3 immune-related adverse event that is considered to be related to atezolizumab or requires atezolizumab to be withheld for > 42 days, unless approved by the Medical Monitor
- Any adverse event that meets criteria for permanent discontinuation per guidelines provided in Section 5.1

- Disease progression

  Because of the potential for tumor flares with immunotherapies, resulting in early apparent radiographic progression (pseudoprogression/tumor immune infiltration), including the appearance of new lesions followed by delayed response (Wolchok et al. 2009), patients whose CT scans meet the criteria for disease progression may continue to receive study treatment at the discretion of the investigator and following discussion with the Medical Monitor, if certain criteria are met (see Section 4.1 for details). Cases of delayed pseudoprogression have also been described in patients with solid tumors treated with immunotherapies. In case of CT- findings suggestive for pseudoprogression in patients with persistent clinical benefit, the investigator should contact the Medical Monitor to discuss further patient management. Patients who continue to receive study treatment should have a CT scan repeated 4–8 weeks later.

- Pregnancy

In case of toxicity solely attributable to one drug of the combination requiring discontinuation, the other study drugs may be continued for patients experiencing clinical benefit as determined by the investigator after discussion with the Medical Monitor.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Patients who discontinue study treatment will not be replaced, except as outlined below:

- During the dose-escalation phase, patients who discontinue study treatment prior to completing the DLT assessment window for reasons other than a DLT will be replaced by an additional patient at that same dose level.
- During the expansion phase, patients who discontinue study treatment prior to receiving at least one dose of each component of the combination will be replaced.

4.6.3 Study and Site Discontinuation

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

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

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 on Harmonisation (ICH) guideline for GCP
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with study treatment components in completed and ongoing studies. The anticipated important safety risks of IMPs in this study (i.e., obinutuzumab, rituximab, atezolizumab, and polatuzumab vedotin) are outlined below. Refer to the Obinutuzumab, Rituximab, Atezolizumab, and Polatuzumab Vedotin Investigator's Brochures for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this trial. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1). In addition, patients will undergo adequate safety monitoring during the study, as described in this section and in Section 4.5. Finally, guidelines for managing adverse events, including criteria for dosage modification and treatment delays or discontinuation, have been provided (see Section 5.1.6).

5.1.1 Risks Associated with Obinutuzumab

The following adverse events are considered to be important risks associated or potentially associated with obinutuzumab: IRRs, hypersensitivity reactions, TLS, neutropenia (including prolonged and late onset neutropenia), thrombocytopenia (including acute thrombocytopenia), infections (including PML and HBV reactivation), prolonged B-cell depletion, impaired immunization response, worsening of preexisting cardiac conditions, GI perforation, immunogenicity, and second malignancies. These events, with the exception of prolonged B-cell depletion, immunogenicity, and second malignancies, are described below.

5.1.1.1 Infusion-Related Reactions

IRRs have been reported predominantly during the first infusion of obinutuzumab. The incidence and severity of IRRs decreased substantially with the second and subsequent infusions. In the majority of patients, IRRs were mild or moderate and resolved with the slowing or interruption of the infusion and supportive care. The commonly experienced IRRs have been characterized by nausea, fatigue, chills, hypotension, fever, vomiting, dyspnea, flushing, hypertension, headache, tachycardia, dizziness, diarrhea, and other symptoms.

IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions; anaphylaxis has been reported in patients treated with obinutuzumab.

Hypotension may occur during obinutuzumab IV infusions. Therefore, withholding of anti-hypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication.

Patients who have preexisting cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the postinfusion period.

Guidelines for medical management of IRRs and anaphylaxis are provided in Section 4.3.2.1 and Appendix 9.

5.1.1.2 Hypersensitivity Reactions

Hypersensitivity reactions with immediate (e.g., anaphylaxis) and delayed onset (e.g., serum sickness) have been reported in patients treated with obinutuzumab. Hypersensitivity reactions typically occur after previous exposure and very rarely with the first infusion. If a hypersensitivity reaction is suspected during or after an infusion, the infusion should be stopped and treatment permanently discontinued.

5.1.1.3 Tumor Lysis Syndrome

The TLS, including fatal events, has been reported with obinutuzumab administration. Patients at risk for TLS (e.g., because of bulky disease or renal insufficiency) should receive adequate hydration and premedication with allopurinol or an alternative uricostatic agent as indicated in Section 4.3.2.7 (see Table 9). Additional guidelines for management of TLS in this study are provided in Section 5.1.6.

5.1.1.4 Neutropenia

Grade 3 or 4 neutropenia, including febrile neutropenia, has been reported with obinutuzumab administration. Neutropenia resolved spontaneously or with use of hematopoietic growth factors. Patients who experience Grade 3 or 4 neutropenia should be closely monitored until neutrophil values return to at least Grade 2. Cases of late-onset neutropenia (ANC <1000 cells/μL occurring ≥ 28 days after obinutuzumab treatment has been completed or stopped) or prolonged neutropenia (ANC <1000 cells/μL that does not resolve after 28 days without obinutuzumab treatment) have also been reported. Prophylactic treatment with antibiotics should be administered as per standard practice. The use of G-CSF is allowed for treatment of neutropenia in this study. Guidelines for primary prophylaxis with G-CSF are provided in Section 4.3.2.7.

5.1.1.5 Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. In patients with CLL exposed to obinutuzumab, fatal hemorrhagic events have also been reported in Cycle 1. A clear relationship between thrombocytopenia and

hemorrhagic events has not been established. Patients receiving concomitant medication that could possibly worsen thrombocytopenia related events (e.g., platelet inhibitors and anticoagulants) may be at greater risk of bleeding. When possible, replace prior vitamin K antagonist therapy with LMWH prior to Day 1 of Cycle 1. Patients should be closely monitored for thrombocytopenia, especially during the first cycle. For patients who experience thrombocytopenia, 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) may be performed at the discretion of the treating physician, according to institutional practice.

5.1.1.6 Infections

On the basis of its mechanism of action, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Obinutuzumab should not be administered to patients with active infection, and caution should be exercised when including patients with a history of recurrent or chronic infections.

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported.

In the Gallium study (BO21223), a high incidence of infections was observed in all phases of the study (81%), including follow-up (19%), with the highest incidence observed during maintenance (70%) in recipients of obinutuzumab and chemotherapy. During the follow-up phase, Grade 3–5 infections (12%) were observed more in patients who received obinutuzumab plus bendamustine in the induction phase.

Reactivation of hepatitis B in patients with chronic hepatitis (HBsAg positive) with evidence of prior hepatitis B exposure or in patients who are carriers (HBsAg negative and HBcAb positive) has been reported with other anti-CD20 antibodies. The risk is increased particularly when anti-CD20 antibodies are administered with immunosuppressive therapies, such as steroids or chemotherapy. Patients who are positive for HBsAg and HBcAb are not eligible for this study.

JC viral infection resulting in PML has been reported in patients treated with 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 symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs or symptoms regarded as "cortical" (e.g., aphasia or visual-spatial disorientation) may 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). Additional guidelines for medical management of PML in this study are provided in Section 5.1.6.

5.1.1.7 Immunizations

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

5.1.1.8 Worsening of Pre-existing Cardiac Conditions

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.

5.1.1.9 Gastrointestinal Perforation

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

5.1.2 Risks Associated with Rituximab

The following adverse events are considered to be important risks associated or potentially associated with rituximab: An IRRs, infections (including PML and HBV reactivation), neutropenia (including prolonged neutropenia), TLS, impaired immunization response, severe skin reactions, and GI perforation. Details for these risks are provided below; refer to Rituximab Investigator's Brochure for full information.

5.1.2.1 Infusion-Related Reactions

Acute IRRs are very common in patients receiving rituximab (occurring in $\geq 10\%$ of patients) based on clinical trial experience. However, serious IRRs are uncommonly reported (occurring in ≥ 1 of 1,000 and < 1 of 100 patients) and are rarely fatal (occurring in ≥ 1 of 10,000 and < 1 of 1,000 patients). Most IRRs occur with the first administration of rituximab. Rituximab-induced IRRs consist of a cluster of symptoms and signs occurring during or within 24 hours of a rituximab infusion which may be related to cytokine release and/or other chemical mediators, and these acute IRRs overlap with "cytokine release syndrome." Anaphylactic and other hypersensitivity reactions have been reported following rituximab administration, and clinical manifestations of these reactions are similar to cytokine release syndrome. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the rituximab infusion.

5.1.2.2 Infections (Including Serious Infections)

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.

5.1.2.3 Hepatitis B Reactivation

Reactivation of hepatitis B ranges from asymptomatic reactivations (detected by changes in laboratory parameters only) to fulminant liver failure and death. 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 and Bennett 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 it 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 patients' last infusion of rituximab.

5.1.2.5 Neutropenia

Neutropenia is very common in patients receiving rituximab (occurring in $\geq$10% of patients) based on clinical trial experience. However, delayed onset neutropenia is very rare (occurring in $<$1 of 10,000 patients), and the incidence of prolonged neutropenia is unknown. Neutropenia may lead to serious or overwhelming infection, especially if profound (Grade 3–4), prolonged, associated with breaches in natural mucosal barriers (e.g., diarrhea and/or mucositis), and/or other immunological defects (e.g., lymphopenia, hypogammaglobulinemia, and acquired immunodeficiency syndrome). Despite an increase in incidence of neutropenia and Grade 3–4 neutropenia associated with rituximab, most studies have not reported a significant increase in serious neutropenic infections.

5.1.2.6 Tumor Lysis Syndrome

Patients treated with rituximab may be at risk for TLS. Severe tumor TLS is very rare in patients receiving rituximab (occurring in $<$1 of 10,000 patients), based on postmarketing experience. Signs and symptoms (e.g., hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated LDH) that are consistent with TLS have been reported to occur after the first MabThera/Rituxan IV infusion in patients with high numbers of circulating malignant lymphocytes. A high number of circulating malignant cells ($\geq$25,000/mm3) or high tumor burden confers a greater risk of TLS. For patients with evidence of TLS, rituximab should be discontinued, and the patient should be treated as clinically indicated.

5.1.2.7 Impaired Immunization Response

B-cell depletion is expected (and desired) during rituximab therapy and is directly related to its mechanism of action. In theory, peripheral B-cell depletion may reduce the effectiveness of immunization, since patients may not be able to mount an effective humoral immune response to foreign antigens.

5.1.2.8 Severe Skin Reactions

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. The onset of these reactions in patients treated with rituximab has varied from 1–13 weeks following rituximab exposure. The majority of the TEN/SJS cases reported with rituximab were associated with additional risk factors. Fatal outcome also appeared to increase in patients who were exposed to multiple risk factors for TEN/SJS.

5.1.2.9 Gastrointestinal 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 GI perforation was 6 days (range: 1–77 days) in patients with NHL.

5.1.3 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, hypophysitis, myocarditis, and nephritis. In addition, systemic immune activation is a potential risk when atezolizumab is given in combination with other immunomodulating agents. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Guidelines for management of atezolizumab-associated non-hematologic toxicity are provided in Table 14 and Table 15.

5.1.4 Risks Associated with Polatuzumab Vedotin

The clinical safety profile of polatuzumab vedotin based on clinical data obtained in the ongoing Phase I and II studies is summarized in Section 1.4. On the basis of clinical data to date, the following identified and potential risks are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.6. Refer also to the current Polatuzumab Vedotin Investigator's Brochure for complete and updated details.

5.1.4.1 Identified Risks for Polatuzumab Vedotin

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

Neutropenia

Neutropenia and neutropenia-associated events resulted in protocol-mandated dose reductions and/or delays. Serious neutropenia including febrile neutropenia has been reported during treatment with polatuzumab vedotin. Patients with inadequate hematologic function will be excluded from this study (see Section 4.1.2). Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Treatment may be delayed for hematologic toxicities as described in Section 5.1.6. The G-CSF may be administered for neutropenia as described in Section 4.3.2.7.

Peripheral Neuropathy

Patients receiving polatuzumab vedotin may develop or experience worsening of peripheral neuropathy. Patients in clinical trials with polatuzumab vedotin should be monitored for symptoms of neuropathy (sensory and/or motor), including hypoesthesia, hyperesthesia, paresthesia, dysesthesia, discomfort, a burning sensation, weakness, gait disturbance, or neuropathic pain. Patients experiencing new or worsening peripheral neuropathy may require a dose delay, change in dose, or discontinuation of treatment and should be managed according to the protocol. Study treatment dose and schedule modifications for peripheral neuropathy are described in Section 5.1.6.

5.1.4.2 Potential Risks for Polatuzumab Vedotin

Infections

Reports in the literature state that granulocytopenia is a major predisposing factor to infections in patients with B-cell lymphoma. Patients receiving chemotherapy for B-cell lymphoma with a granulocyte count of <500 cells/μL experienced a higher incidence of infections than those with a count of >500 cells/μL.

Progressive Multifocal Leukoencephalopathy

[redacted]

[redacted]

Infusion-Related Events

Because of the potential for infusion reactions, administration of polatuzumab vedotin will be performed in a setting with access to emergency equipment and staff who are trained to monitor and respond to medical emergencies. All patients will be monitored for infusion reactions during the infusion and immediately afterward (for additional instructions on the monitoring and management of infusion reactions, see Section 4.3.2.3). Precautions for suspected anaphylactic reaction during study drug infusions are provided in Section 4.3.2.3. The initial dose of polatuzumab vedotin may be administered with premedication with acetaminophen, antihistamines, or corticosteroids per institutional standard practice at the discretion of the Investigator. Premedication should be instituted for subsequent doses if IRRs are observed in patients who receive their first dose of polatuzumab vedotin without premedications (see Section 4.3.2.3). Significant issues with polatuzumab vedotin IRRs have not been observed.

Tumor Lysis Syndrome

There is the potential risk of TLS if treatment with polatuzumab vedotin results in the rapid destruction of a large number of tumor cells. If any evidence of this occurs during the study, tumor lysis prophylaxis measures will be instituted. Patients who are considered to have a high tumor burden (e.g., bulky lymphadenopathy) and who are considered to be at risk for tumor lysis by the investigator will receive tumor lysis prophylaxis (e.g., allopurinol $\geq$ 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 on Day 1 of Cycle 1. Patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration before each subsequent infusion, as deemed appropriate by the investigator.

Bone Marrow Toxicity

Patients with inadequate hematologic function will be excluded from this study (see Section 4.1.2). Patients receiving study treatment will be regularly monitored for evidence of marrow toxicity with complete blood counts. Treatment may be delayed for hematologic toxicities as described in Section 5.1.6.

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

Immunogenicity

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

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.

Specific Gastrointestinal Toxicity

Diarrhea, constipation, anorexia, nausea, and vomiting have been reported frequently as treatment-emergent adverse events in studies DCS4968g and GO27834 with polatuzumab vedotin. Diarrhea has been responsible for study drug modification and discontinuations.

Hyperglycemia

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

Hepatotoxicity

Hepatotoxicity has been observed in patients treated with polatuzumab vedotin in both the Phase I and II trials. Although the relationship between hepatotoxicity and polatuzumab vedotin has not been definitively determined, transient, dose-related increases in hepatic enzymes were noted in nonclinical rat studies. No hepatotoxicity was noted following administration of the surrogate ADC in cynomolgus monkeys. Elevations of transaminases have been reported in patients receiving polatuzumab vedotin and have ranged in intensity from Grades 1–3. These have been reversible with and without dose modification.

5.1.5 Risk of Overlapping Toxicities and Drug-Drug Interactions

As with any experimental regimen, there is a risk of unexpected/unknown toxicities that may occur during the study. Two patients with RR FL treated with obinutuzumab, atezolizumab, and polatuzumab vedotin experienced the concomitant occurrence of severe and difficult-to-treat dermatitis, oral mucositis, and ocular events refractory to standard treatment with corticosteroids. The severity and the concomitant observation of this constellation of events is not consistent with the safety profile of the individual drugs (see Section 5.1.6), and hence constitutes an unexpected safety signal.

Hematologic toxicity (mainly neutropenia) is the most common toxicity associated with obinutuzumab, rituximab, and polatuzumab vedotin. The risk of overlapping hematologic toxicity with the addition of atezolizumab to obinutuzumab/rituximab and polatuzumab vedotin is expected to be low. There is no expectation for the combination to enhance the risk of peripheral sensory neuropathy associated with polatuzumab vedotin. Considering the risk associated with each individual component of the combination (Section 5.1.1, Section 5.1.3, and Section 5.1.4), the expected overlapping non-hematologic toxicities are IRRs, infections, skin rash, GI toxicity, and hepatotoxicity/elevated liver transaminases. Additionally, there is an identified risk of TLS with obinutuzumab and rituximab and a potential risk with polatuzumab vedotin because these agents can result in the rapid destruction of a large number of tumor cells. Therefore, overlapping toxicity in regard to TLS cannot be excluded. Guidelines for management of patients who develop TLS are provided in Table 14.

The risk of clinically relevant PK DDIs is low between obinutuzumab/rituximab, atezolizumab, and polatuzumab vedotin. Obinutuzumab/rituximab and polatuzumab vedotin are known to deplete or decrease circulating B cells and tumor burden, which may potentially affect the target-mediated clearance of obinutuzumab and polatuzumab vedotin. However, in relapsed or refractory FL and DLBCL, the baseline B-cell count is low; therefore, the likelihood of B-cell–mediated pharmacokinetic DDI is relatively low. This hypothesis is supported by preliminary results from the ongoing Study GO27834 in relapsed or refractory FL and DLBCL, where no interaction was observed between polatuzumab vedotin and rituximab.

In addition, the risk of CYP- and P-gp–mediated DDI between obinutuzumab/rituximab atezolizumab, and polatuzumab vedotin is considered low, as addressed below.

Obinutuzumab, rituximab, atezolizumab, and the antibody component of polatuzumab vedotin are therapeutic proteins, and are therefore not anticipated to interact directly with CYP isoforms or other drug-metabolizing enzymes or drug transporters. Cytokine modulation may be considered as an indirect mechanism through which a monoclonal antibody could alter CYP expression. For this treatment combination however, the unconjugated MMAE component of polatuzumab vedotin is considered the only moiety that could potentially be affected by a DDI involving this indirect mechanism. Administration of obinutuzumab results in merely transient increases in cytokine levels after the first infusion, and no increases are observed after subsequent infusions. Preclinical studies with anti-CD79 antibodies showed a low risk for release of systemic pro-inflammatory cytokines (Schmidt and Wittrup 2009). In vitro data indicate that atezolizumab is unlikely to induce cytokine release. Taken together, these results suggest that obinutuzumab/rituximab, atezolizumab, and polatuzumab vedotin are unlikely to precipitate DDIs via indirect effects on cytokines.

Simulation results based on a physiologically-based PK model (Chen et al. 2015) suggest that unconjugated MMAE exposure is unlikely to be altered by $>$50% when

polatuzumab vedotin is co-administered with strong CYP3A inhibitors or inducers and MMAE is unlikely to cause a DDI effect on other CYP substrates, supporting a low probability for a clinically significant DDI with unconjugated MMAE. However, patients who receive concomitant medications that are strong CYP3A or P-gp inhibitors should be closely monitored for adverse reactions.

The potential for ATA-mediated DDIs among study treatment agents is considered low because the treatment combination is anticipated to deplete B-cells, and thus reduce the body's ability to produce ATAs.

5.1.6 Concomitant Skin, Oral Mucosa, and Ocular Toxicity Observed in Patients with RR FL Treated with G+Atezo+Pola

Two patients with RR FL treated with obinutuzumab, atezolizumab, and polatuzumab vedotin experienced a concomitant severe dermatitis, oral mucositis, and ocular toxicities in the form of scleritis and conjunctivitis, respectively, partially responding to standard treatment with high dose corticosteroids. T-cell infiltration was observed in the skin biopsy of these 2 patients. Whereas the exact mechanism underlying the concomitant occurrence of severe dermatitis, oral mucositis, and ocular toxicities is unknown; there may be an increased risk for patients to develop immune adverse events derived from the combination of these drugs by activation of the immune effectors. Atezolizumab was discontinued in all patients still receiving study treatment due to the perceived contribution to the clinical findings, through its mode of action.

The concomitant occurrence of severe and difficult-to-treat dermatitis, oral mucositis, and ocular toxicities in these 2 patients is not consistent with the safety profile of the individual drugs (refer to the Investigator's Brochures of the individual drugs). In addition, no similar combination of toxicities has been observed in ongoing studies evaluating atezolizumab+obinutuzumab and obinutuzumab/rituximab+polatuzumab vedotin. Hence, this unique T-cell, immune-mediated toxicity was assessed as specifically related to the combination of obinutuzumab, atezolizumab, and polatuzumab vedotin.

Patients should be monitored carefully for any signs or symptoms of immune-related events including dermatitis, mucositis, and ocular toxicities.

5.1.7 Management of Specific Adverse Events

Study treatment may be delayed for toxicity for a maximum amount of time, as specified in the tables below. If study treatment is delayed for longer than the specified maximum, study treatment will be permanently discontinued.

Treatment delays apply to all toxicities described below; dose modifications apply only to polatuzumab vedotin in the event of neurotoxicity (see Table 14 and Table 16). There will be no dose reductions of obinutuzumab or atezolizumab.

Guidelines for management of systemic immune activation are provided in Section 5.1.7.1. Guidelines for management of toxicities during induction are provided in Section 5.1.7.2. Guidelines for management of toxicities during post-induction are provided in Section 5.1.7.3.

5.1.7.1 Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, this condition is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

Table 11 Diagnostic Criteria and Recommended Management for Systemic Immune Activation

Systemic Immune Activation Diagnostic Criteria (applicable only when alternative etiologies have been excluded)	
Major Criteria	Minor Criteria
• Fever ≥38.5°C on more than one occasion • Ferritin ≥3000 ng/mL • Cytopenias (Grade ≥2 in two or more lineages) • Age-adjusted soluble IL-2 receptor elevated by ≥2 standard deviations • Severe dysfunction in two or more organs • Decreased fibrinogen	• Splenomegaly • Hemophagocytosis in bone marrow, spleen, or lymph nodes • Elevated GGT or LFTs (AST, ALT, or total bilirubin) • Elevated triglycerides • Elevated LDH • Decreased natural killer cell activity

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken
≥4 major criteria	Consistent with systemic immune activation	• Permanently discontinue atezolizumab. • Consider treatment with tocilizumab (4 mg/kg IV) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent). • Contact the Medical Monitor for additional recommendations. • Consider HLH-94 protocol if there is no clinical improvement.
3 major criteria OR 2 major plus ≥3 minor criteria	Probable systemic immune activation	• Depending on clinical severity, follow guidelines for "Consistent with systemic immune activation" or "Possible systemic immune activation" diagnosis. • The Medical Monitor may be contacted for recommendations.
2 major plus ≤2 minor criteria OR 1 major plus ≥4 minor criteria	Possible systemic immune activation	• Withhold atezolizumab. • Consider treatment with IV corticosteroids. • The Medical Monitor may be contacted for additional recommendations. • Follow guidelines for "Consistent with systemic immune activation" diagnosis if there is no clinical improvement or if clinical worsening occurs. • If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor.

GGT = γ-glutamyl transpeptidase; IL-2 = interleukin-2; IV = intravenous; LFT = liver function test.

Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014). Case reports and recommendations have been published for cytokine-release syndrome (Teachey et al. 2013; Maude et al. 2014), and, on the basis of etiologic similarities, these practices have been incorporated into the above treatment recommendations. These recommendations do not replace clinical judgment and are intended as suggested guidance.

An adverse event of systemic immune activation should be reported on the Adverse Event eCRF if it meets the criteria for "consistent with systemic immune activation" or "probable systemic immune activation" as outlined above in Table 11.

5.1.7.2 Toxicities during Induction Treatment

Hematologic Toxicities during Induction Treatment

Table 12 provides guidelines for management of hematologic toxicities that occur during induction treatment, with the exception of Days 8 and 15 of Cycle 1.

Table 13 provides guidelines for management of hematologic toxicities that occur at Days 8 and 15 of Cycle 1, when patients are to receive treatment with obinutuzumab only.

Hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia. Lymphopenia is not considered a hematologic toxicity but rather an expected outcome of therapy.

Table 12 Guidelines for Management of Hematologic Toxicities that Occur during Induction Treatment (Except Days 8 and 15 of Cycle 1)

Event	Action To Be Taken
Grade 3 or 4 hematologic toxicity	• Withhold study treatment. [a] • Administer RBCs or platelets as required. • If patient has not already initiated G-CSF, initiate prophylactic G-CSF for current and subsequent cycles. • For patients receiving primary thromboprophylaxis who develop platelet count of $<20{,}000/\mu L$, reduce the dose of LMWH or consider temporarily withholding platelet inhibitors, as applicable. If the patient's condition doesn't allow for reduction of the LMWH dose or interruption of platelet inhibitor treatment, adequate platelet transfusion support and close monitoring of hematologic and coagulation functions are required. • If there is improvement to Grade ≤ 2 or baseline by Day 1 of the next cycle or ≤ 21 days after the scheduled start date of the next cycle, resume obinutuzumab/rituximab, and polatuzumab vedotin at full dose. • If study treatment is withheld for >21 days, permanently discontinue study treatment. • Permanently discontinue study treatment if any of the following events occur: – Grade 3 or 4 thrombocytopenia that results in significant bleeding per investigator judgment – Recurrent Grade 3 or 4 neutropenia associated with fever $>38°C$ lasting >5 days or documented infection despite use of G-CSF – Recurrent Grade 4 neutropenia or thrombocytopenia lasting >7 days despite use of G-CSF (for neutropenia)

G-CSF = granulocyte colony-stimulating factor; LMWH = low-molecular-weight heparin.

[a] For neutropenia, treatment should be withheld only for sustained (≥ 7 days) Grade 3 neutropenia or Grade ≥ 3 neutropenia associated with fever (temperature $\geq 38.5°C$).

Table 13 Guidelines for Management of Hematologic Toxicities That Occur on Days 8 and 15 of Cycle 1

Event	Action to Be Taken
Febrile neutropenia or neutropenia with infection	• Withhold obinutuzumab until resolution of fever and infection (as applicable). • If the event is ongoing at Day 1 Cycle 2, follow instructions in Table 12. Note: Obinutuzumab should not be withheld for asymptomatic neutropenia.
Severe thrombocytopenia [a] or bleeding	• Withhold obinutuzumab until platelet count ≥50,000/μL and resolution of bleeding. • If receiving LMWH, reduce the dose. • If receiving platelet inhibitors, consider temporarily withholding platelet inhibitors. • If the event is ongoing at Day 1 Cycle 2, follow instructions in Table 12.

LMWH = low-molecular-weight heparin.

[a] Severe thrombocytopenia is defined as a platelet count < 10,000/μL for patients who are not receiving concomitant anticoagulants or platelet inhibitors and < 20,000/μL for patients who are receiving concomitant anticoagulants or platelet inhibitors.

Non-Hematologic Toxicities during Induction Treatment

Table 14 provides guidelines for management of non-hematologic toxicities that occur during induction treatment.

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology. For detailed information regarding management of adverse events associated with atezolizumab, refer to the Atezolizumab Investigator's Brochure.

Table 14 Guidelines for Management of Non-Hematologic Toxicities

Event	Action To Be Taken
General guidance for treatment delays and discontinuation	• For patients receiving obinutuzumab, if toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses of obinutuzumab will not be skipped but given after resolution of toxicity. • When a treatment cycle is delayed because of a toxicity resulting from any component of the regimen, all study treatment should generally be held and resumed together to remain synchronized. • If one drug is discontinued, treatment with the other two drugs may be continued for patients experiencing clinical benefit as determined by the investigator after discussion with the Medical Monitor. • Permanently discontinue study treatment if any of the following events occur: – Grade ≥3 non–immune-related adverse event that is considered to be treatment related and does not resolve to Grade ≤2 within 21 days – Non–immune-related adverse event that is considered to be treatment related and requires study treatment to be withheld for >21 days
IRRs and anaphylaxis	• Guidelines for the management of IRRs are provided in Section 4.3.2.1 for obinutuzumab, Section 4.3.2.2 for atezolizumab, Section 4.3.2.3 for polatuzumab vedotin, and Section 4.3.2.4 for rituximab. • Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis. • In case of anaphylaxis, study treatment should be permanently discontinued.
Systemic immune activation	• Follow guidance in Section 5.1.7.1 .
TLS	• Withhold study treatment until symptoms completely resolve. Perform chemistry panel on a regular bases during the first week. • Correct electrolyte abnormalities, monitor renal function, cardiac function and fluid balance, and administer supportive care, including dialysis as indicated. Rasburicase therapy (if approved by the local health authority) may be administered as needed to reduce hyperuricemia. • If symptoms resolve completely, obinutuzumab/rituximab, and polatuzumab vedotin may be resumed at full dose.

Table 14 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Dermatologic toxicity	Grade 4	• Permanently discontinue study treatment.
	Grade 3	First occurrence • Withhold study treatment. • Consult with a dermatologist. A biopsy should be considered unless contraindicated. • If immune etiology is suspected, consider oral prednisone 10 mg or equivalent. If event is unresolved after 48–72 hours, administer oral prednisone 60 mg or equivalent. • If there is improvement to Grade ≤ 1, resume obinutuzumab/rituximab and polatuzumab vedotin at full dose. • Permanently discontinue obinutuzumab/rituximab and polatuzumab in the event of Stevens-Johnson syndrome or toxic epidermal necrolysis. Second occurrence • Permanently discontinue study treatment.
	Grade 1 or 2	• Continue study treatment • Administer symptomatic therapy with antihistamines as needed • If immune related toxicity related to atezolizumab is suspected, consider topical steroids and, for Grade 2, higher potency topical steroids if rash unresolved.
AST, ALT, or bilirubin increase	Grade ≥ 3 (or $\geq 10 \times$ ULN for patients with liver involvement)	• Withhold study treatment • Monitor liver function tests at least every 7 days while holding treatment. • Investigate etiology. Consult with a hepatologist if immune etiology is suspected (refer to Atezolizumab Investigator's Brochure for guidance on investigations). • For immune related hepatopathy: – Treat with corticosteroids following guidance provided in the Atezolizumab Investigator's Brochure – Obinutuzumab and polatuzumab vedotin may be resumed at full dose at investigator's discretion. • If immune etiology is unlikely and there is improvement to Grade ≤ 1, resume obinutuzumab/rituximab and polatuzumab vedotin at full dose. Permanently discontinue study treatment for life-threatening liver toxicity.

Table 14 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
AST, ALT, or bilirubin increase (cont.)	Grade 2 lasting >5–7 days	• If immune etiology is suspected, treat with corticosteroids according to guidance provided in the Atezolizumab Investigator's Brochure.
Amylase or lipase increase +/-abdominal pain	Grade ≥3	• Withhold study treatment. • Investigate etiology. Consult with a gastroenterologist if immune etiology is suspected. • Treat with corticosteroids according to guidance provided in the Atezolizumab Investigator's Brochure. – If there is improvement to Grade ≤1 and patient is asymptomatic, or improvement to Grade ≤ 2 if lipase or amylase increase is an isolated and asymptomatic laboratory abnormality, resume obinutuzumab/rituximab and polatuzumab vedotin at full dose. • Permanently discontinue study treatment for life-threatening pancreatitis or recurrent Grade 4 amylase or lipase elevations.
	Grade 2 long lasting (>3wks)	• Continue study treatment. • If immune etiology is suspected, consider oral prednisone 10 mg/day or equivalent.
Hyperglycemia	Grade 3–4	• Initiate treatment with insulin. • Monitor for glucose control.
Symptomatic adrenal insufficiency	Grade 2–4	• Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.

Table 14 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Diarrhea/Colitis	Grade 4	• Permanently discontinue study treatment. • Investigate etiology. Consult with a gastroenterologist (refer to Atezolizumab Investigator's Brochure for guidance on investigations in case of suspected immune-related colitis). • Treat with corticosteroids according to guidance provided in the Atezolizumab Investigator's Brochure.
	Grade 2 or 3	• Withhold study treatment. • Investigate etiology. Consult with a gastroenterologist if immune etiology is suspected (refer to Atezolizumab Investigator's Brochure for guidance on investigations). • Treat immune diarrhea/colitis with corticosteroids according to guidance provided in the Atezolizumab Investigator's Brochure. • If diarrhea/colitis improves to Grade $\leq$1, resume obinutuzumab and polatuzumab vedotin at full dose.
Ocular toxicity	Grade 3 or 4	• Withhold obinutuzumab/rituximab and polatuzumab vedotin. • Investigate etiology. Consult with an ophthalmologist. • Treat immune-related toxicity attributable to atezolizumab with systemic corticosteroids according to guidance provided in the Atezolizumab Investigator's Brochure. • If there is improvement to Grade $\leq$ 1, resume obinutuzumab/rituximab and polatuzumab vedotin at full dose.
	Grade 1 or 2	• Investigate etiology. Consult with an ophthalmologist. • Treat with topical corticosteroid eye drops. If symptoms persist, topical immunosuppressive therapy may also be considered.
Hypothyroidism		• Investigate etiology. Consult with an endocrinologist (refer to Atezolizumab Investigator's Brochure for guidance on investigations). • Start thyroid replacement hormone. • Monitor TSH weekly. **For asymptomatic and symptomatic patients with elevation of TSH:** • Continue study treatment.

Table 14 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Hyperthyroidism		**For asymptomatic patients with TSH < 0.5 mU/L:** • Perform TSH, free T4, and T3 tests every 4 weeks. **For asymptomatic patients with TSH < 0.1 mU/L or symptomatic patients:** • Consider consultation with an endocrinologist. • Administer methimazol as needed.
Hypophysitis (panhypopituitarism)	Grade 4	• Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.
	Grade 2 or 3	• Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • For recurrent hypophysitis, treat as a Grade 4 event.
New-onset neurologic manifestations suggestive of PML		• Withhold study treatment. • Consult with a neurologist if PML is suspected (refer to Section 5.1.1.6 for guidance on investigations). • If PML is ruled out, resume obinutuzumab/rituximab and polatuzumab vedotin at full dose. • If PML is confirmed, permanently discontinue study treatment.

Table 14 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Neurotoxicity other than neurologic manifestations suggestive of PML	Grade 4 or Myasthenia gravis (any grade) or Guillain-Barre (any grade)	• Permanently discontinue study treatment.
	Grade 2 or 3	• Withhold study treatment. Investigate etiology. • If neurotoxicity is considered likely related to polatuzumab vedotin and there is improvement to Grade $\leq$1 within 21 days, resume study treatments for subsequent cycles as follows: – Resume obinutuzumab/rituximab at full dose. – For patients who started at 1.8 mg/kg, resume polatuzumab vedotin at a reduced dose of 1.4 mg/kg. For patients who started at 1.4 mg/kg, permanently discontinue polatuzumab vedotin.
Immune-related meningoencephalitis		• Withhold study treatment. • Refer patient to neurologist (see Atezolizumab Investigator's Brochure for guidance on investigations). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade $\leq$1: – Resume obinutuzumab/rituximab at full dose and polatuzumab vedotin at current dose. – Taper corticosteroids over $\geq$1 month.

Table 14 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Immune-related myocarditis	Grade 3–4	• Permanently discontinue study treatment and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over≥1 month. • Investigator might consider continuation of obinutuzumab/rituximab and polatuzumab vedotin, based on an individual benefit-risk assessment, and in consultation with the Medical Monitor.
	Grade 2	• Withhold study treatment. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume study treatment.
	Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.

Table 14 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Immune-related nephritis	*Grade 3 or 4*	• *Permanently discontinue study treatment and contact Medical Monitor.* • *Refer patient to renal specialist.* • *Consider renal biopsy and supportive measures as indicated.* • *Corticosteroids and/or additional immunosuppressive agents should be administered as clinically indicated.* • *If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.*
	Grade 2	• *Withhold atezolizumab for up to 12 weeks after event onset.*[b] *Contact Medical Monitor.* • *Refer patient to renal specialist.* • *Consider renal biopsy and supportive measures as indicated.* • *Corticosteroids and/or additional immunosuppressive agents should be administered as clinically indicated.* • *If event resolves to Grade 1 or better, resume atezolizumab.* [c] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [d]
	Grade 1	• *Continue study treatment.* • *Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.*

Table 14 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Pneumopathy, non-infectious (i.e., dyspnea, hypoxia, pulmonary infiltrates)	Grade 3 or 4	• Withhold obinutuzumab/rituximab and polatuzumab vedotin. • Investigate etiology. Consult with a pulmonologist if immune etiology is suspected (refer to Atezolizumab Investigator's Brochure for guidance on investigations). • Treat immune related pneumopathy with corticosteroids according to guidance provided in the Atezolizumab Investigator's Brochure. • If symptoms have resolved and CT lung findings are clear, obinutuzumab and polatuzumab vedotin may be resumed at full dose.
	Grade 2	• Treat with corticosteroids according to guidance provided in the Atezolizumab Investigator's Brochure.
Other non-hematologic and non-immune-related toxicities (i.e., not described above), excluding alopecia, nausea, and vomiting	Grade 4	• Permanently discontinue study treatment.
	Grade 2 or 3	• Withhold study treatment. • If there is improvement to Grade $\leq$ 1 or baseline, resume obinutuzumab/rituximab and polatuzumab vedotin at current dose. • In case of laboratory abnormalities that are isolated, asymptomatic, and considered not clinically significant: – For Grade 3 laboratory abnormalities, study treatment may be resumed at the current dose upon improvement to at least Grade 2. – For Grade 2 laboratory abnormalities, study treatment may be continued at the current dose at the investigator's discretion.

Table 14 Guidelines for Management of Non-Hematologic Toxicities (cont.)

CT = computed tomography; ECMO = extracorporeal membrane oxygenation; IRR = infusion-related reaction; PML = progressive multifocal leukoencephalopathy; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = nonsteroidal anti-inflammatory drug; TLS = tumor lysis syndrome; TSH = thyroid-stimulating hormone; ULN = upper limit normal; VAD = ventricular assist device.

[a] Graded according to NCI CTCAE Version 3.0.

[b] *Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.*

[c] *If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.*

[d] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

5.1.7.3 Toxicities during Maintenance Treatment

Table 15 provides guidelines for management of toxicities that occur during maintenance treatment.

Table 15 Guidelines for Management of Toxicities that Occur during Maintenance Treatment

Event	Action To Be Taken
Hematologic toxicity: Grade 3 or 4	• Withhold obinutuzumab/rituximab. • Administer G-CSF for neutropenia per institutional guidelines. • Administer RBCs or platelets as required. • If there is improvement to Grade ≤2, resume obinutuzumab at full dose. • If obinutuzumab is withheld for >42 days due to adverse event, permanently discontinue obinutuzumab/rituximab.
Non-hematologic toxicity: Grade ≥ 2	**For atezolizumab-related toxicities with possible immune etiology[1]:** • Follow guidelines presented in Table 14 for the management of atezolizumab-related toxicities with possible immune etiology (i.e., autoimmune colitis, hepatitis, pancreatitis, hypothyroidism, hyperthyroidism, pneumopathy, skin toxicity, or ocular toxicity). **For non-immune mediated toxicities:** • Withhold study treatment. • If there is improvement to Grade ≤1 or baseline, resume obinutuzumab/rituximab at full dose. • If study treatment is withheld for >42 days due to adverse event, permanently discontinue study treatment.

G-CSF = granulocyte colony-stimulating factor.

[1] Please refer to atezolizumab Investigators Brochure for additional information.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH guideline for 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 treatment
- 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 SAE is any adverse event that meets any of the following criteria:

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

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

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

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

The SAEs 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 adverse events of special interest listed below.

Adverse events of special interest to any study drug are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, 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 any of the study treatment components is suspected.

Adverse events of special interest to obinutuzumab are as follows:

- TLS of any grade of severity, and irrespective of causality
- Second malignancies

Adverse events of special interest to atezolizumab are as follows:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 x ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis

- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis

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

During the DLT assessment window (Cycles 1 and 2), adverse events identified as DLTs, as defined in Section 3.1.2.1.1, are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.5 Selected Adverse Events

Adverse events of special interest are listed in Section 5.2.3. Selected adverse events in this study are defined as adverse events for which additional data collection or analyses will be performed. Selected adverse events do not require immediate reporting if they are not serious (except for TLS and second malignancies).

The following adverse events are considered selected adverse events:

- Thrombocytopenia, including acute thrombocytopenia (events occurring during and within 24 hours following obinutuzumab infusion)
- Hepatitis B reactivation
- Cardiac events
- IRRs
- All infections, including PML
- Neutropenia, including prolonged neutropenia (neutropenia < 1000 cells/μL that does not resolve after 28 days without obinutuzumab treatment) and late-onset neutropenia (neutropenia < 1000 cells/μL occurring ≥ 28 days after obinutuzumab treatment has been completed or stopped)
- GI perforation
- Peripheral neuropathy (motor and/or sensory)

Events for which additional data collection will be required are PML, Hepatitis B and Hepatitis B reactivation.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study treatment**, only SAEs 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 SAEs).

After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment. After this period, the investigator should report any SAEs that are believed to be related to prior study treatment (see Section 5.6).

An exception is made for Grade 3 or 4 infections (related and unrelated to study treatment), which should be reported until up to 2 years after the last dose of obinutuzumab (G+Atezo+ Pola treatment group).

Similarly, second malignancies (related and unrelated to study treatment) will be reported indefinitely (even if the study has been closed) for patients who received obinutuzumab (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity, with the exception of tumor flare reactions, which will be graded using NCI CTCAE v3.0. Table 16 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

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

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

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

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event, considering especially the effects of study treatment modifications or discontinuation, or reintroduction of study treatment (as applicable)
- Known association of the event with the study treatment 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

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 the end of study treatment infusion and are judged to be related to infusion of any of the study treatment components should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of lymphoma should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An 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").

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

5.3.5.9 Preexisting Medical Conditions

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

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When

recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Lymphoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the Lugano 2014 criteria (see Appendix 5). 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 SAEs (per the definition of SAEs 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 treatment administration or insertion of access device for study treatment 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 Adverse Events Associated with an Overdose or Error in Treatment Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events

associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No experience with overdosage is available from human clinical trials. In clinical trials with obinutuzumab doses ranging from 50 mg up to and including 2000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose-dependent.

Patients who experience overdose should have immediate interruption or reduction of their infusion and should be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- The SAEs (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- DLTs (see Section 5.2.4 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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 SAEs to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], Ph.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 Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

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

5.4.2.2 Events That Occur after Study Treatment Initiation

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

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

Instructions for reporting post-study 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 18 months after the last

dose of study treatment for patients in the G + Atezo + Pola (FL) treatment group and within 12 months after the last dose of study treatment for patients in the R + Atezo + Pola (DBCL) treatment group. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment 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 SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be

classified as a SAE, 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 SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

For SAEs, 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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF.

An exception is made for Grade 3 and 4 infections (related and unrelated to prior study treatment), which should be reported until up to 2 years after the last dose of study treatment.

The Sponsor should also be notified of events of second malignancies indefinitely (related and unrelated to study treatment, even if the G+Atezo+pola treatment group or the overall study has been closed) for patients who received obinutuzumab.

If the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper

Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- Obinutuzumab Investigator's Brochure
- Atezolizumab Investigator's Brochure
- Polatuzumab Vedotin Investigator's Brochure
- Rituximab Investigator's Brochure

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 study will include an initial dose-escalation phase followed by an expansion phase in relapsed or refractory FL patients; and a safety run-in phase followed by an expansion phase in relapsed or refractory DLBCL patients. The dose-escalation phase is designed to determine the RP2D for polatuzumab vedotin when combined with fixed doses of obinutuzumab and atezolizumab in patients with relapsed or refractory FL. During the expansion phase, patients with relapsed or refractory FL will undergo treatment with polatuzumab vedotin at the RP2D, obinutuzumab, and atezolizumab; and patients with relapsed or refractory DLBCL will undergo treatment with polatuzumab vedotin 1.8 or 1.4 mg/kg, rituximab, and atezolizumab.

Study data will be summarized separately for each phase. Data from the dose-escalation phase will be summarized by each polatuzumab vedotin dose cohort. Data from the expansion phase will be summarized by histologic subtype (i.e., FL or DLBCL).

6.1 DETERMINATION OF SAMPLE SIZE

Limited dose-finding will be conducted during the dose-escalation phase of polatuzumab vedotin in combination with obinutuzumab and atezolizumab. The estimated sample size follows from the dose-escalation rules for a standard 3+3 algorithm, as outlined in Section 3.1.

A total of 9 patients with RR FL were enrolled in the dose-escalation phase (3 patients in the Pola 1.4-mg dose cohort and 6 patients in the Pola 1.8-mg dose cohort), and a total of 7 patients with RR DLBCL were enrolled into the safety run-in phase and treated with 1.8 mg polatuzumab vedotin. During the expansion phase, 34–40 patients with DLBCL and 34–37 patients with FL (for a total of 40 patients with FL at RP2D in the dose-escalation and expansion phases) were planned to be enrolled. Overall, approximately 83–92 patients were planned to be enrolled in the study. As of 1 March 2018, 13 patients with RR FL and 23 patients with RR DLBCL were enrolled in the study.

The primary efficacy analysis will be the estimation of the true proportion of patients expected to obtain a PET-CT–defined CR at EOI.

6.2 DEFINITION OF ANALYSIS POPULATIONS

For both the safety and efficacy analyses, the following populations are defined:

- The primary population will include patients who received at least 1 dose of each component of the combination.
- The intent-to-treat population will include all patients enrolled in the study.

Patients with FL who receive polatuzumab vedotin at the RP2D during the dose-escalation phase will be pooled with patients who receive polatuzumab vedotin at the RP2D during the expansion phase.

6.3 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol violations, and discontinuations from the study will be listed. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated.

Data related to the administration of study treatment components will be listed, and any dose modifications will be flagged. The number of doses, treatment cycles, average dose received, and relative dose intensity for each treatment component will be summarized using descriptive statistics (mean, standard deviation, median, and range).

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics by treatment group, such as age, sex, race, and duration of malignancy, will be summarized using descriptive statistics (mean,

standard deviation, median, and range) for continuous variables and frequencies and percentages for categorical variables.

6.5 SAFETY ANALYSES

The safety analyses will be performed by treatment group, separately for each study phase (i.e., dose-escalation and expansion). The main analysis for safety will include data until end of study. Additionally, a censoring will be applied as of 1 March 2018 to the safety analyses, to evaluate the effect of the triplet drug combination in each treatment group. The sensitivity analysis will be based on the censored safety dataset and will include data from patients as of 1 March 2018 plus the 90-day safety reporting window (see Section 5.3.1). Patients enrolled and who have not received any treatment with atezolizumab will be analyzed separately by treatment group, G+Pola and R+Pola.

Safety will be assessed through summaries of adverse events, changes from baseline in laboratory test results, and laboratory data with values outside of the normal ranges.

All adverse events occurring on or after the first dose of study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 grade. All SAEs, adverse events of special interest, and selected adverse events will be summarized and listed.

Deaths reported during the treatment period and during post-treatment follow-up will be listed.

Relevant laboratory results will be displayed by time, with Grade 3 and 4 values identified as appropriate.

6.6 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all patients enrolled in the expansion phase, and will be performed by treatment group. In addition, patients with FL who received polatuzumab vedotin at the RP2D during the dose-escalation phase will be pooled for analysis with patients with FL treated in the expansion phase. Patients with DLBCL from the safety run-in phase will be pooled for analysis with patients with DLBCL treated in the expansion phase at the same polatuzumab vedotin dose. A censoring will be applied as of 1 March 2018 to the efficacy analyses, to evaluate the effect of the triplet drug combination in each treatment group. The efficacy analysis will be performed on the censored efficacy dataset, and will include data from patients as of 1 March 2018 plus the corresponding assessment time window (see Appendix 1 and Appendix 2).

6.6.1 Primary Efficacy Endpoint

The primary efficacy analysis will be estimation of the proportion of patients achieving a CR at EOI, as determined by the investigator through use of the PET-CT-based Lugano 2014 criteria (see Appendix 5). Point estimates will be presented, along with the

corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without a post-baseline tumor assessment will be considered non-responders.

6.6.2 Secondary Efficacy Endpoints

The secondary efficacy analyses will be estimation of the proportion of patients achieving each of the following endpoints:

- CR at EOI, as determined by the investigator on the basis of CT scans alone
- Objective response (defined as a CR or PR) at EOI, as determined by the investigator on the basis of PET-CT scans
- Objective response (defined as a CR or PR) at EOI, as determined by the investigator on the basis of CT scans alone
- Best response of CR or PR during the study, as determined by the investigator on the basis of CT scans alone

Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without a post-baseline tumor assessment will be considered non-responders.

6.6.3 Exploratory Efficacy Endpoints

Exploratory efficacy analyses will include estimation of the proportion of patients achieving each of the following endpoints:

- For FL patients who have positive PET scans at EOI: CR at 12 months, as determined by the investigator on the basis of PET-CT scans

Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without a post-baseline tumor assessment will be considered non-responders.

OS will be summarized descriptively using the Kaplan-Meier method (Kaplan and Meier 1958). For the OS analysis, data for patients who have not died will be censored at the date the patient was last known to be alive. Where medians are reached, the corresponding estimated median will be provided, along with the 95% CI using the method of Brookmeyer and Crowley (1982).

6.7 PHARMACOKINETIC ANALYSES

Plasma or serum concentrations of obinutuzumab, rituximab, atezolizumab, and polatuzumab vedotin will be tabulated, summarized, and plotted after appropriate grouping. As appropriate, PK parameters (e.g., AUC, time to maximum concentration, maximum concentration, and half-life) may also be calculated, tabulated, and summarized after appropriate grouping. Additional PK and PK/PD analyses (e.g., population modeling, including pooled analyses across studies) may also be performed as appropriate. If done, these additional analyses may be reported separately from the Clinical Study Report.

6.8 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one predose and one postdose HAHA, HACA or ATA assessment.

The numbers and proportions of post-treatment HAHA-, HACA- or ATA-positive patients and HAHA-, HACA- or ATA-negative patients at baseline and during both the treatment and follow-up periods will be summarized. The relationship between HAHA, HACA or ATA status and safety, efficacy, and PK endpoints will be explored as appropriate.

6.9 BIOMARKER ANALYSES

Exploratory analyses of biomarkers related to tumor biology and study treatment mechanisms of action will be conducted. Analyses will assess the prognostic and/or predictive value of candidate biomarkers with respect to investigator-assessed outcomes. Specifically, the association between candidate biomarkers and PET-CT–defined CR rate and OR rate, and potentially other measures of efficacy and safety, will be explored to assess potential prognostic or predictive value. These analyses may not be included in the final study report because of their exploratory nature. In addition to analysis in the context of this study, data will also be explored in aggregate with data from other studies.

6.10 INTERIM ANALYSES

No interim analyses are planned and review of safety and/or efficacy data by the IMC may be requested by and carried out at the discretion of the Medical Monitor. Further details regarding the rules and guidelines of data review will be provided in an IMC charter.

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 any other externally-generated electronic study data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

The 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.

7.2 ELECTRONIC CASE REPORT FORMS

The 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. The 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. The 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 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, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

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

No records 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.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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 (defined as the time when all enrolled patients with FL have completed or discontinued study treatment and all enrolled patients with DLBCL have been followed for at least 1 year after they have completed or discontinued study treatment.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd.

The EDC 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 4.5.7; otherwise, local laboratories will be used. A central independent review facility will be used to collect PET-CT and CT scans. Data from this study will be shared with an Expert Scientific Committee that will provide scientific input for the benefit-risk assessment.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all

requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://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 Assessments for Patients with Follicular Lymphoma

	Screening [a]		Induction (6 months; 21-day cycles)				EOI	Maint. (24 months)		EOM [b]	90-Day Safety FU Visit (at 3 Months) [d]	*Survival FU Period (Q3M)[kk]*
	D −28 to D −1	D −14 to D −1	Cycle 1 (±1 days)			Cycles 2–6 (±2 days)	After Last Induction Dose [c]	Monthly (±1 wk)	Every 2 months (±1 wk)	35 days after Last Dose		
			D1	D8	D15	D1		D1	D1			
Informed consent [e]												
Demographic data	x											
Medical history	x											
ECOG Performance Status	x											
Vital signs [f]	x		x	x	x	x	x	x	x	x		
Height	x											
Weight	x		x			x						
12-lead ECG	x						x [g]			x		
Complete physical examination [h, i]	x											
Targeted physical examination [i, j]						D1, Cycles 2 and 4	x		x	x	x	
Ann Arbor, FLIPI, and FLIPI2	x											
B symptoms [k]	x											
β_2 microglobulin		x										
Hematology [l]		x	x [m,n]	x [n]	x [n]	x [n] (C2: D1, D8, D15	x [g]	x [n]	x	x		
Chemistry panel (serum or plasma) [o]		x	x [m,n]	x [n]	x [n]	x [n]	x [g]	x [n]	x	x		
Coagulation (INR, aPTT [or PTT], and PT)		x										
Pregnancy test		x [p]				x [p]	x [g]			x		
Hepatitis B and C testing [q]	x											
TSH, T3, T4	x		Every 3 months									
Quantitative IgA, IgG, IgM			x				x	x [r]	x	x	x	

Appendix 1
Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

	Screening [a]		Induction (6 months; 21-day cycles)				EOI	Maint. (24 months)		EOM [b]	90-Day Safety FU Visit (at 3 Months) [d]	*Survival FU Period (Q3M)* [kk]
	D −28 to D −1	D −14 to D −1	Cycle 1 (±1 days)			Cycles 2–6 (±2 days)	After Last Induction Dose [c]	Monthly (±1 wk)	Every 2 months (±1 wk)	35 days after Last Dose		
			D1	D8	D15	D1		D1	D1			
HAHA sample for obinutuzumab			x [s]									
ATA sample for atezolizumab and polatuzumab vedotin			x [s]									
PK sample for obinutuzumab, atezolizumab and polatuzumab vedotin			x [s]									
Plasma for soluble PD-L1			x [n]									
Whole blood for lymphocyte immunophenotyping [t]			x [n]			x [n]	x	x [r]		x	x	
Whole blood for T-cell receptor repertoire in PBMCs			x [n]			x [n, u]	x	x [v]				
Plasma for cytokine analysis			x [n]			x [n, u]						
Optional peripheral blood sample for RCR [w]			x [n]									
Tumor tissue specimen (leftover tissue may be used for optional RCR specimen [v])	x [x]					x [y]	x [y]					
Concomitant medications [z]	x [z]		To be recorded continually until end of treatment [z]									
Adverse events [aa]	x [aa]		To be assessed continually [aa]									
PET-CT scan	x [bb]						x [cc]	x [dd]				
CT scan [ee]	x [ee]					x [ff]	x [cc]	x [ff]		x [gg]		
Bone marrow biopsy and aspirate	x [hh]						x [cc, ii]	x [ii]		x [hh, ii]		

Appendix 1
Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

		Screening [a]		Induction (6 months; 21-day cycles)				EOI	Maint. (24 months)		EOM [b]	90-Day Safety FU Visit (at 3 Months) [d]	*Survival FU Period (Q3M)[kk]*
		D −28 to D −1	D −14 to D −1	Cycle 1 (±1 days)			Cycles 2–6 (±2 days)	After Last Induction Dose [c]	Monthly (±1 wk)	Every 2 months (±1 wk)	35 days after Last Dose		
				D1	D8	D15	D1		D1	D1			
Study treatment administration	Obinutuzumab [jj]			x	x	x	x			x			
	Polatuzumab vedotin [jj]			x			x						
New anti-lymphoma treatment												*x*	*x*
Survival follow-up													*x*

ATA = anti-therapeutic antibody; C = Cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOI = end of induction; EOM = end of maintenance; FLIPI = Follicular Lymphoma International Prognostic Index; FU = follow-up; HAHA = human anti-human antibody; Maint. = maintenance; MRD = minimal residual disease; MRI = magnetic resonance imaging; NK = natural killer; PBMC = peripheral blood mononuclear cell; PET = positron emission tomography; PK = pharmacokinetic; Q3M = every 3 months; RCR = Roche Clinical Repository; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; wk = week. Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] The screening period starts with the signing of the Informed Consent Form. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the defined window may be used as screening and baseline assessments; such tests do not need to be repeated for screening purposes.

[b] Patients who complete maintenance treatment or discontinue maintenance treatment prematurely will undergo assessments at EOM.

[c] EOI assessments should be performed 6–8 weeks after Day 1 of the last induction cycle. As an exception, patients who discontinue induction treatment prematurely because of an adverse event may undergo EOI assessments 4–8 weeks after their last dose of study treatment.

[d] Patients who complete treatment or prematurely discontinue treatment for reasons other than disease progression will undergo assessments at the 90-day safety follow-up visit.

[e] Informed consent must be documented before any study-specific screening procedure is performed.

Appendix 1
Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

[f] Vital signs include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For obinutuzumab infusions: For the first cycle, second cycle, and for patients who experience an infusion-related reaction, vital signs will be measured prior to the infusion, every 15 (±5) minutes for the first 90 minutes of the infusion, and then every 30 (±10) minutes until 1 hour after completion of the infusion. For subsequent cycles, vital signs will be measured every 30 minutes during the infusion, except in patients who had experienced an infusion-related reaction during a prior infusion. For polatuzumab vedotin infusions: 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 at Cycle 2, and 30 (±10) minutes following completion of dosing in subsequent cycles.

[g] Perform only in patients who will not be receiving maintenance treatment.

[h] 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.

[i] As part of tumor assessment, the physical examination should include evaluation for the presence of enlarged nodes, palpable hepatomegaly, and splenomegaly. This information will be recorded on the appropriate tumor assessment eCRF.

[j] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Unexplained fever $>38°C$, night sweats, and unexplained weight loss $>10\%$ of body weight over 6 months.

[l] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[m] Screening laboratory assessments may be used for Day 1 of Cycle 1 if performed within 72 hours prior to Day 1 of Cycle 1.

[n] Perform hematology and chemistry tests within 72 hours prior to Day 1 of each cycle during induction or every 2 months during maintenance, and within 24 hours prior to other timepoints during induction treatment. Samples for exploratory biomarker research should be collected at the same time as hematology and chemistry samples.

[o] Includes sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, glycosylated hemoglobin (HbA_{1c}), amylase, lipase, LDH, and uric acid. HbA_{1c} will be measured only at screening and can be obtained in a non-fasting state.

[p] All women of childbearing potential will have a serum pregnancy test at screening, within 7 days prior to Day 1 of Cycle 1. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[q] Includes hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody.

[r] Perform at the same time as tumor assessments at 12, 18, and 24 months after initiation of induction treatment.

[s] See Appendix 3 for detailed schedule.

[t] Includes B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK cell counts (CD16 and CD56).

[u] Cycles 2 and 3 only.

[v] Perform at the same time as tumor assessments at 12 and 18 months after initiation of induction treatment.

[w] Requires separate patient consent for RCR participation. Not applicable for a site that has not been granted approval for RCR sampling.

[x] Availability of adequate archival or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.7 for details).

[y] A tumor biopsy sample will be collected prior to the start of Cycle 2 and at the time of progression unless no adequate tumor site is accessible.

[z] 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 the screening period until the EOI or EOM visit, whichever occurs later.

[aa] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment (see Section 5.6). An exception is made for Grade 3 or 4 infections (related and unrelated), which should be reported until up to 2 years after the last dose of obinutuzumab. 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 any of the study treatment components or trial-related procedures until a final outcome can be reported.

[bb] The screening PET-CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[cc] Perform only for patients who have received at least two cycles of induction treatment.

[dd] If PET-CT scan is positive at EOI, perform at 12 months after initiation of induction treatment, within 14 days prior to treatment administration.

[ee] Includes CT scan of the neck (if clinically indicated), chest, abdomen, and pelvis. If contrast is medically contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans of the chest, abdomen, and pelvis (and neck, if clinically indicated) and a non-contrast CT scan of the chest may be performed. Combined PET/CT scanners may be used to collect diagnostic CT scans, but only according to the technical guidelines in the imaging manual. The screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

Appendix 1
Schedule of Assessments for Patients with Follicular Lymphoma (cont.)

[ff] Perform within 7 days prior to Day 1 of Cycle 3, and at 12, 18, and 24 months after initiation of induction treatment, within 14 days prior to treatment administration. Patients with radiographic evidence of progression at the end of Cycle 2 who continue to receive study treatment per criteria defined in Section 3.1.1 should have a CT scan repeated 4–8 weeks later.

[gg] Perform only if not done within the previous 3 months.

[hh] Bone marrow biopsy and aspirate must be performed within approximately 3 months prior to Day 1 of Cycle 1.

[ii] For patients with bone marrow involvement at screening, a repeat assessment will be performed at EOI if there is radiologic evidence of a complete response, and during maintenance or at EOM if there is radiologic evidence of a complete response or if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression).

[jj] Refer to Sections 4.3.2.5 and Section 4.3.2 for details on dosing and schedule.

[kk] *Patients who experience disease progression or discontinued study treatment will be evaluated for survival status and new anti-lymphoma treatment every 3 months until the end of the study. The end of the study is defined as the time when all enrolled patients with FL have completed or discontinued study treatment and all enrolled patients with DLBCL have been followed for at least 1 year after they have completed or discontinued study treatment.*

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma

	Screening [a]		Induction (6 months; 21-day cycles)		EOI	90-Day Safety FU Visit (at 3 Months) [c]	*Survival FU Period (Q3M)* [ee]
	D –28 to D –1	D –14 to D –1	Cycle 1 (± 1 day) D1	Cycles 2–6 (± 2 days) D1	After Last Induction Dose [b]		
Informed consent [d]	x						
Demographic data	x						
Medical history	x						
ECOG Performance Status	x						
Vital signs [e]	x		x	x	x		
Height	x						
Weight	x		x	x			
12-lead ECG	x				x		
Complete physical examination [f, g]	x						
Targeted physical examination [g, h]				D1, C2 and C4	x	x	
Ann Arbor and IPI	x						
B symptoms [i]	x						
β2 microglobulin		x					
Hematology [j]		x	x [k, l]	x [l] (C2: D1, D8, D15)	x		
Chemistry panel (serum or plasma) [m]		x	x [k, l]	x [l]	x		
Coagulation (INR, aPTT [or PTT], and PT)		x					
Pregnancy test		x [n]		x [n]	x		
Hepatitis B and C testing [o]	x						
TSH, T3, T4	x		Every 3 months				
Quantitative IgA, IgG, IgM			x		x	x	
HACA sample for rituximab			x [p]				

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma (cont.)

		Screening [a]		Induction (6 months; 21-day cycles)		EOI	90-Day Safety FU Visit (at 3 Months) [c]	*Survival FU Period (Q3M)[ee]*
		D −28 to D −1	D −14 to D −1	Cycle 1 (±1 day) D1	Cycles 2–6 (±2 days) D1	After Last Induction Dose [b]		
ATA sample for atezolizumab and polatuzumab vedotin				x [p]				
PK sample for rituximab, atezolizumab and polatuzumab vedotin				x [p]				
Plasma for soluble PD-L1				x [l]				
Whole blood for lymphocyte immunophenotyping [q]				x [l]	x [l]	x	x	
Whole blood for T-cell receptor repertoire in PBMCs				x [l]	x [l, r]	x		
Plasma for cytokine analysis				x [l]	x [l, r]			
Optional peripheral blood sample for RCR [s]				x [l]				
Tumor tissue specimen (leftover tissue may be used for optional RCR specimen [s])		x [t]			x [u]	x [u]		
Concomitant medications		x [v]		To be recorded continually until end of treatment [v]				
Adverse events [w]		x [w]		To be assessed continually [w]				
PET-CT scan		x [x]				x [y]		
CT scan [z]		x [z]			x [aa]	x [y]		
Bone marrow biopsy and aspirate		x [bb]				x [y, cc]		
Study treatment administration	Rituximab [dd]			x	x			
	Polatuzumab vedotin [dd]			x	x			
New anti-lymphoma treatment							*x*	
Survival follow-up								

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma (cont.)

ATA = anti-therapeutic antibody; C = Cycle; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOI = end of induction; FU = follow-up; HAHA = human anti-human antibody; IPI = International Prognostic Index; MRI = magnetic resonance imaging; NK = natural killer; PBMC = peripheral blood mononuclear cell; PET = positron emission tomography; PK = pharmacokinetic; Q3M = every 3 months; RCR = Roche Clinical Repository; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; wk = week.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] The screening period starts with the signing of the Informed Consent Form. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the defined window may be used as screening and baseline assessments; such tests do not need to be repeated for screening purposes.

[b] EOI assessments should be performed 6–8 weeks after Day 1 of the last induction cycle. As an exception, patients who discontinue induction treatment prematurely because of an adverse event may undergo EOI assessments 4–8 weeks after their last dose of study treatment.

[c] Patients who complete treatment or prematurely discontinue treatment for reasons other than disease progression will undergo assessments at the 90-day safety follow-up visit.

[d] Informed consent must be documented before any study-specific screening procedure is performed.

[e] Vital signs include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For rituximab infusions: Vital signs monitoring during infusion should be determined as per local label. For polatuzumab vedotin infusions: 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 at Cycle 2, and 30 (±10) minutes following completion of dosing in subsequent cycles.

[f] 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.

[g] As part of tumor assessment, the physical examination should include evaluation for the presence of enlarged nodes, palpable hepatomegaly, and splenomegaly. This information will be recorded on the appropriate tumor assessment eCRF.

[h] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Unexplained fever > 38°C, night sweats, and unexplained weight loss > 10% of body weight over 6 months.

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma (cont.)

[j] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[k] Screening laboratory assessments may be used for Day 1 of Cycle 1 if performed within 72 hours prior to Day 1 of Cycle 1.

[l] Perform hematology and chemistry tests within 72 hours prior to Day 1 of each cycle during induction and within 24 hours prior to other timepoints during induction treatment. Samples for exploratory biomarker research should be collected at the same time as hematology and chemistry samples.

[m] Includes sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, glycosylated hemoglobin (HbA_{1c}), amylase, lipase, LDH, and uric acid. HbA_{1c} will be measured only at screening and can be obtained in a non-fasting state.

[n] All women of childbearing potential will have a serum pregnancy test at screening, within 7 days prior to Day 1 of Cycle 1. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[o] Includes hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody.

[p] See Appendix 4 for detailed schedule.

[q] Includes B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK-cell counts (CD16 and CD56).

[r] Cycles 2 and 3 only.

[s] Requires separate patient consent for RCR participation. Not applicable for a site that has not been granted approval for RCR sampling.

[t] Availability of adequate archival (obtained within 6 months prior to the initiation of study treatment) or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.7 for details).

[u] A tumor biopsy sample will be collected prior to the start of Cycle 2 and at the time of progression unless no adequate tumor site is accessible.

[v] 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 the screening period until the EOI visit.

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

[x] The screening PET-CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[y] Perform only for patients who have received at least two cycles of induction treatment.

Appendix 2
Schedule of Assessments for Patients with Diffuse Large B-Cell Lymphoma (cont.)

[z] Includes CT scan of the neck (if clinically indicated), chest, abdomen, and pelvis. If contrast is medically contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans of the chest, abdomen, and pelvis (and neck, if clinically indicated) and a non-contrast CT scan of the chest may be performed. Combined PET/CT scanners may be used to collect diagnostic CT scans, but only according to the technical guidelines in the imaging manual. The screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[aa] Perform within 7 days prior to Day 1 of Cycle 3. Patients with radiographic evidence of progression at the end of Cycle 2 who continue to receive study treatment per criteria defined in Section 3.1.1 should have a CT scan repeated 4–8 weeks later.

[bb] Bone marrow biopsy and aspirate must be performed within approximately 3 months prior to Day 1 of Cycle 1.

[cc] For patients with bone marrow involvement at screening, a repeat assessment will be performed at EOI if there is radiologic evidence of a complete response or if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression).

[dd] Refer to Sections 4.3.2.5 and Section 4.3.2 for details on dosing and schedule.

[ee] *Patients who experience disease progression or discontinued study treatment will be evaluated for survival status and new anti-lymphoma treatment every 3 months until the end of the study. The end of the study is defined as the time when all enrolled patients with FL have completed or discontinued study treatment and all enrolled patients with DLBCL have been followed for at least 1 year after they have completed or discontinued study treatment.*

Appendix 3
Pharmacokinetic and Immunogenicity Sampling Schedule for Obinutuzumab, Atezolizumab, and Polatuzumab Vedotin

Study Visit		Serum Obinutuzumab PK Sample [a,b]	Serum Atezolizumab PK Sample [a]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a]	Plasma Polatuzumab Vedotin PK Sample for Antibody-Conjugated MMAE and Unconjugated MMAE [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Atezolizumab ATA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Induction (Cycles 1–6; 21-day cycles)								
Cycle 1	Day 1	Prior to infusion (any time prior to dose); 30±10 minutes after end of infusion [d]	—	Prior to infusion (any time prior to dose)	Prior to infusion (any time prior to dose) 30±10 minutes after end of infusion	Prior to infusion (any time prior to dose)	—	Prior to infusion (any time prior to dose)
	Day 8	—	—	—	Anytime during visit	—	—	—
	Day 15	—	—	—	Anytime during visit	—	—	—
Cycle 2	Day 1	Prior to infusion (within 5 hr prior to dose) 30±10 minutes after end of infusion	—	Prior to infusion (within 5 hr prior to dose)	Prior to infusion (within 5 hr prior to dose); 30±10 minutes after end of infusion	—	—	Prior to infusion (any time prior to dose)
Cycle 3	Day 1	—	—	—	—	—	—	
Cycle 4	Day 1	Prior to infusion (within 5 hr prior to dose); 30±10 minutes after end of infusion	—	Prior to infusion (within 5 hr prior to dose)	Prior to infusion (within 5 hr prior to dose); 30±10 minutes after end of infusion	—	—	Prior to infusion (any time prior to dose)
Cycle 6	Day 1	Prior to infusion (within 5 hr prior to dose); 30±10 minutes after end of infusion	—	—	Prior to infusion (within 5 hr prior to dose)	Prior to infusion (any time prior to dose)	—	—

Appendix 3
Pharmacokinetic and Immunogenicity Sampling Schedule for Obinutuzumab, Atezolizumab, and Polatuzumab Vedotin (cont.)

Study Visit		Serum Obinutuzumab PK Sample [a,b]	Serum Atezolizumab PK Sample [a]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a]	Plasma Polatuzumab Vedotin PK Sample for Antibody-Conjugated MMAE and Unconjugated MMAE [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Atezolizumab ATA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Maintenance (Months 1–24)								
Month 1	Day 1	Prior to infusion (within 5 hr prior to dose)	—	Prior to infusion (within 5 hr prior to dose)	—	—	—	—
	Day 2	—	—	—	—	—		—
Month 4	Day 1	—	—	—	—	—	—	—
Months 7, 13, and 19	Day 1	Prior to infusion (within 5 hr prior to dose)	—	—	—	—	—	—
Discontinuation and Follow-Up [b, c]								
Treatment discontinuation		Anytime during visit	Anytime during visit	Anytime during visit	—	Anytime during visit	Anytime during visit	Anytime during visit
120 ± 30 days after last dose of obinutuzumab, polatuzumab and atezolizumab (as appropriate for sample)		Anytime during visit	Anytime during visit	Anytime during visit	—	Anytime during visit	Anytime during visit	Anytime during visit

ATA = anti-therapeutic antibody; HAHA = human anti-human antibody; PK = pharmacokinetic.

[a] Sample collection timing is relative to specified drug.

[b] Samples collected for PK, HAHA, and ATA analysis may be used for additional PK, HAHA, and/or ATA assay development and validation and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] The sampling applies once study treatment is discontinued for a given molecule (obinutuzumab, atezolizumab, or polatuzumab vedotin), irrespective of the study phase when discontinuation occurs (ie, induction or maintenance).

[d] If the Cycle 1 Day 1 dose of obinutuzumab is split over two days, take the 30 and ±10 minutes post end of infusion obinutuzumab PK sample after the end of the 900mg infusion on Day 2, and ensure that the date and time of the PK collection are accurately recorded.

Appendix 4
Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Atezolizumab, and Polatuzumab Vedotin

Study Visit		Serum Rituximab PK Sample [a,b]	Serum Atezolizumab PK Sample [a]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a]	Plasma Polatuzumab Vedotin PK Sample for Antibody-Conjugated MMAE and Unconjugated MMAE [a]	Serum Rituximab HACA Sample [a]	Serum Atezolizumab ATA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Induction (Cycles 1–6; 21-day cycles)								
Cycle 1	Day 1	Prior to infusion (any time prior to dose); 30 ± 10 minutes after end of infusion [d]	—	Prior to infusion (any time prior to dose)	Prior to infusion (any time prior to dose) 30 ± 10 minutes after end of infusion	Prior to infusion (any time prior to dose)	—	Prior to infusion (any time prior to dose)
Cycle 2	Day 1	Prior to infusion (within 5 hr prior to dose)	—	Prior to infusion (within 5 hr prior to dose)	Prior to infusion (within 5 hr prior to dose); 30 ± 10 minutes after end of infusion	Prior to infusion (any time prior to dose)	—	Prior to infusion (any time prior to dose)
Cycle 3	Day 1	—	—	—	—	—	—	—
Cycle 4	Day 1	Prior to infusion (within 5 hr prior to dose)	—	Prior to infusion (within 5 hr prior to dose)	Prior to infusion (within 5 hr prior to dose) 30 ± 10 minutes after end of infusion	Prior to infusion (any time prior to dose)	—	Prior to infusion (any time prior to dose)
Cycle 6	Day 1	Prior to infusion (within 5 hr prior to dose); 30 ± 10 minutes after end of infusion	—	—	Prior to infusion (within 5 hr prior to dose)	Prior to infusion (any time prior to dose)	—	—

Appendix 4
Pharmacokinetic and Immunogenicity Sampling Schedule for Rituximab, Atezolizumab, and Polatuzumab Vedotin (cont.)

Study Visit	Serum Rituximab PK Sample [a,b]	Serum Atezolizumab PK Sample [a]	Serum Polatuzumab Vedotin PK Sample for Total Antibody [a]	Plasma Polatuzumab Vedotin PK Sample for Antibody-Conjugated MMAE and Unconjugated MMAE [a]	Serum Rituximab HACA Sample [a]	Serum Atezolizumab ATA Sample [a]	Serum Polatuzumab Vedotin ATA Sample [a]
Discontinuation and Follow-Up[b, c]							
Treatment discontinuation	Anytime during visit	Anytime during visit	Anytime during visit	—	Anytime during visit	Anytime during visit	Anytime during visit
120 (±30 days) after last dose of rituximab, polatuzumab and atezolizumab (as appropriate for sample)	Anytime during visit	Anytime during visit	Anytime during visit	—	Anytime during visit	Anytime during visit	Anytime during visit
1 year after last dose of polatuzumab vedotin	—	—	Anytime during visit	—	—	—	Anytime during visit

ATA = anti-therapeutic antibody; HACA = human anti-chimeric antibody; PK = pharmacokinetic.

[a] Sample collection timing is relative to specified drug.

[b] Samples collected for PK, HACA, and ATA analysis may be used for additional PK, HACA, and ATA assay development and validation and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] The sampling applies once study treatment is discontinued for a given molecule (rituximab, atezolizumab, or polatuzumab vedotin), irrespective of the study phase when discontinuation occurs (i.e., induction).

[d] If the Cycle 1 Day 1 dose of rituximab is split over two days, take the 30 and ±10 minutes post end of infusion rituximab PK sample after the end of the rituximab infusion on Day 2, and ensure that the date and time of the PK collection are accurately recorded.

Appendix 5
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

In this study, the Lugano 2014 criteria for a PET-CT–based complete response (CR) and partial response (PR) have been modified, as outlined below:

- A designation of PET-CT–based CR requires normal bone marrow by morphology for patients with bone marrow involvement at baseline. If indeterminate by morphology, immunohistochemistry should be negative.
- A designation of PET-CT–based PR requires that CT-based response criteria for a CR or PR be met in addition to the PET-CT–based response criteria for a PR.

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

Appendix 5
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

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

Appendix 5
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least one of the following
Individual target nodes/nodal masses	Score 4 or 5 [b] with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi $>$ 1.5 cm and Increase by $\geq$ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions $\leq$ 2 cm 1.0 cm for lesions $>$ 2 cm In the setting of splenomegaly, the splenic length must increase by $>$ 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to $>$ 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisting non-measured lesions

Appendix 5
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; 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). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured; dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

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

REFERENCE

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;32:3059–69.

Appendix 6
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active Able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities Up and about >50% of waking hours
3	Capable of only limited self-care; confined to a bed or chair >50% of waking hours
4	Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

Appendix 7
Ann Arbor Staging

Grade	Description
Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE) [a]
Stage II	Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIIES)
Stage IV [b]	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

Note: All cases are subclassified to indicate the absence (A) or presence (B) of the systemic B symptoms of significant unexplained fever (> 38°C), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

[a] The designation "E" generally refers to extranodal contiguous extension (i.e., proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. A single extralymphatic site as the only site of disease should be classified as IE, rather than Stage IV.

[b] Involvement of bone marrow at screening will always qualify for Ann Arbor Stage IV and should be recorded as extranodal involvement.

Adapted from:

Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971;31:1860–1.

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds Meeting. J Clin Oncol 1989;7:1630–6.

Appendix 8
Follicular Lymphoma International Prognostic Index

Table 1 Follicular Lymphoma International Prognostic Index

FLIPI Risk Factor
Ann Arbor Stage III or IV
Age >60 years
Serum LDH $>1\times$ 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 to 5

FDG = fluorodeoxyglucose; FLIPI = Follicular Lymphoma International Prognostic Index; PET = positron emission tomography; ULN = upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of FLIPI since 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.

Table 2 Follicular Lymphoma International Prognostic Index 2

FLIPI2 Risk Factor
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 to 5

FDG = fluorodeoxyglucose; FLIPI2 = Follicular Lymphoma International Prognostic Index 2; PET = positron emission tomography; ULN = upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of FLIPI2 since 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 9
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous (IV), and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

PROCEDURES

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

- Stop the study treatment infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer glucocorticoids, antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 10
Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below will be excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, patients with transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Dermatomyositis	Neuromyotonia
Addison's disease	Diabetes mellitus type 1	Opsoclonus myoclonus syndrome
Ankylosing spondylitis	Dysautonomia	Optic neuritis
Antiphospholipid antibody syndrome	Epidermolysis bullosa acquista	Ord's thyroiditis
Aplastic anemia	Gestational pemphigoid	Pemphigus
Autoimmune hemolytic anemia	Giant cell arteritis	Pernicious anemia
Autoimmune hepatitis	Goodpasture's syndrome	Polyarteritis nodusa
Autoimmune hypoparathyroidism	Graves' disease	Polyarthritis
Autoimmune hypophysitis	Guillain-Barré syndrome	Polyglandular autoimmune syndrome
Autoimmune myocarditis	Hashimoto's disease	Primary biliary cirrhosis
Autoimmune oophoritis	IgA nephropathy	Psoriasis
Autoimmune orchitis	Inflammatory bowel disease	Reiter's syndrome
Autoimmune thrombocytopenic purpura	Interstitial cystitis	Rheumatoid arthritis
Behcet's disease	Kawasaki's disease	Sarcoidosis
Bullous pemphigold	Lambert-Eaton myasthenia syndrome	Scleroderma
Chronic inflammatory demyelinating polyneuropathy	Lupus erythematosus	Sjögren's syndrome
Chung-Strauss syndrome	Lyme disease - chronic	Stiff-Person syndrome
Crohn's disease	Meniere's syndrome	Takayasu's arteritis
	Mooren's ulcer	Ulcerative colitis
	Morphea	Vitiligo
	Multiple sclerosis	Vogt-Kovanagi-Harada disease
	Myasthenia gravis	Wegener's granulomatosis
	Myasthenia gravis	

Appendix 11
Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine clearance (men)} = \frac{(140 - \text{Age}) \times \text{Lean body weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine clearance (women)} = \frac{0.85 \times (140 - \text{Age}) \times \text{Lean body weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Adapted from: Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine [editorial]. Nephron 1992;62:249–56.