Official Title: A Phase IB/II Study Evaluating the Safety and Efficacy of Atezolizumab in Combination With Either Obinutuzumab Plus Bendamustine or Obinutuzumab Plus CHOP in Patients With Follicular Lymphoma or Rituximab Plus CHOP in Patients With Diffuse Large B-Cell Lymphoma

NCT Number: NCT02596971

Document Date: Protocol Version 6: 07-November-2018

PROTOCOL

TITLE: **A PHASE IB/II STUDY EVALUATING THE SAFETY AND EFFICACY OF ATEZOLIZUMAB IN COMBINATION WITH EITHER OBINUTUZUMAB PLUS BENDAMUSTINE OR OBINUTUZUMAB PLUS CHOP IN PATIENTS WITH FOLLICULAR LYMPHOMA OR RITUXIMAB PLUS CHOP IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA**

PROTOCOL NUMBER: BO29563

VERSION NUMBER: 6

EUDRACT NUMBER: 2015-001364-19

IND NUMBER: 122847

TEST PRODUCTS: Obinutuzumab (RO5072759)
Rituximab (RO452294)
Atezolizumab (RO5541267)

MEDICAL MONITOR: [redacted], Ph.D.

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version 1: 13 May 2015

DATE AMENDED: Version 2: 23 October 2015
Version 3: 7 September 2016
Version 4: 26 May 2017
Version 5: 22 December 2017
Version 6: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	07-Nov-2018 02:09:35

CONFIDENTIAL

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

Protocol BO29563 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 with atezolizumab in combination with obinutuzumab plus CHOP or with atezolizumab in combination with rituximab plus CHOP, once all patients have completed/discontinued study treatment (maintenance/consolidation), 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 3.1.3).
- Post-trial access language was changed allowing patients still under study treatment to enter an extension study in case of earlier closure of Study BO29563 (Section 4.3.4).
- The Medical Monitor information has been updated (Section 5.4.1).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE IB/II STUDY EVALUATING THE SAFETY AND EFFICACY OF ATEZOLIZUMAB IN COMBINATION WITH EITHER OBINUTUZUMAB PLUS BENDAMUSTINE OR OBINUTUZUMAB PLUS CHOP IN PATIENTS WITH FOLLICULAR LYMPHOMA OR RITUXIMAB PLUS CHOP IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA**
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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 at Covance.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IB/II STUDY EVALUATING THE SAFETY AND EFFICACY OF ATEZOLIZUMAB IN COMBINATION WITH EITHER OBINUTUZUMAB PLUS BENDAMUSTINE OR OBINUTUZUMAB PLUS CHOP IN PATIENTS WITH FOLLICULAR LYMPHOMA OR RITUXIMAB PLUS CHOP IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	BO29563
VERSION NUMBER:	6
EUDRACT NUMBER:	2015-001364-19
IND NUMBER:	122847
TEST PRODUCTS:	Obinutuzumab (RO5072759) Rituximab (RO452294) Atezolizumab (RO5541267)
PHASE:	Phase Ib/II
INDICATION:	Follicular or diffuse large B-cell lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety, efficacy, and pharmacokinetics of induction treatment consisting of atezolizumab in combination with obinutuzumab plus bendamustine (Atezo-G-benda) in patients with follicular lymphoma (FL), atezolizumab in combination with obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (Atezo-G-CHOP) in patients with FL, and atezolizumab in combination with rituximab plus CHOP (Atezo-R-CHOP) in patients with diffuse large B-cell lymphoma (DLBCL), followed by post-induction treatment consisting of either atezolizumab plus obinutuzumab (Atezo-G) in patients with FL who achieve a complete response (CR) or partial response (PR) at end of induction (EOI) or atezolizumab alone in patients with DLBCL who achieve a CR 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 objective for this study is to evaluate the safety and tolerability of induction treatment with either Atezo-G-benda or Atezo-G-CHOP in patients with FL, and Atezo-R-CHOP in patients with DLBCL and post-induction treatment with either Atezo-G in patients with FL or atezolizumab alone in patients with DLBCL on the basis of the following endpoints:

- Nature, frequency, severity, and timing of adverse events
- Changes in vital signs, ECGs, and clinical laboratory results during and following study treatment administration

Efficacy Objectives

Response will be determined through use of the positron emission tomography (PET) and computed tomography (CT)–based Lugano Response Criteria for Malignant Lymphoma, hereinafter referred to as Lugano 2014 criteria. Response will also be determined through use of the modified version of the Revised Response Criteria for Malignant Lymphoma, hereinafter

referred to as modified Cheson 2007 criteria, which take into account both PET-CT and CT scan results. Response will be determined by an Independent Review Committee (IRC) and by the investigator.

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of induction treatment with either Atezo-G-benda or Atezo-R-CHOP, on the basis of the following endpoint:

- CR at EOI, as determined by the IRC using Lugano 2014 criteria

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of induction treatment with either Atezo-G-benda or Atezo-R-CHOP and post-induction treatment with either Atezo-G or atezolizumab alone, on the basis of the following endpoints:

- CR at EOI, as determined by the investigator using Lugano 2014 criteria
- CR at EOI, as determined by the IRC and by the investigator using modified Cheson 2007 criteria
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator using Lugano 2014 criteria and modified Cheson 2007 criteria
- Best response of CR or PR during the study, as determined by the investigator using modified Cheson 2007 criteria

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of induction treatment with either Atezo-G-benda or Atezo-R-CHOP and post-induction treatment with either Atezo-G or atezolizumab alone, on the basis of the following endpoints:

- For patients who have positive PET scans at EOI: CR at 12 months, as determined by the IRC and by the investigator using Lugano 2014 criteria
- CR at 12, 24, and 30 months in patients with previously untreated FL, as determined by the investigator using modified Cheson 2007 criteria
- Progression-free survival, defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by the investigator using modified Cheson 2007 criteria, or death from any cause
- Event-free survival, defined as the time from initiation of study treatment to any treatment failure, including disease progression or relapse, as determined by the investigator using modified Cheson 2007 criteria, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first
- Disease-free survival, defined, among patients achieving a CR, as the time from the first occurrence of a documented CR to relapse, as determined by the investigator using modified Cheson 2007 criteria, or death from any cause, whichever occurs first
- OS, defined as the time from initiation of study treatment to death from any cause

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for this study are to characterize the pharmacokinetics of atezolizumab, rituximab, and obinutuzumab when administered as induction treatment consisting of either Atezo-G-benda, Atezo-G-CHOP, or Atezo-R-CHOP or post-induction treatment consisting of either Atezo-G or atezolizumab alone, on the basis of the following endpoints:

- Observed serum obinutuzumab concentration at specified timepoints
- Observed serum atezolizumab concentration at specified timepoints
- Observed serum rituximab concentration at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab, to rituximab, and to atezolizumab 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 anti-therapeutic antibodies (ATAs) to atezolizumab 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

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:

- Correlation between non-inherited biomarkers and efficacy, safety, PK, or immunogenicity endpoints

Study Design

Description of Study

This Phase Ib/II, open-label, multicenter, non-randomized study will evaluate the safety, efficacy, and pharmacokinetics of combination treatment with atezolizumab, obinutuzumab, and chemotherapy in patients with FL and atezolizumab, rituximab, and chemotherapy in patients with DLBCL.

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

During the safety run-in phase, 12 patients with previously untreated, or relapsed or refractory FL are to be enrolled in either the Atezo-G-benda treatment group (n = 6) or the Atezo-G-CHOP treatment group (n = 6) at the discretion of the investigator. Patients will receive 6 cycles (Cycles 1–6) of induction treatment with either Atezo-G-benda or Atezo-G-CHOP (with atezolizumab starting in Cycle 2 for both treatment groups). Patients who achieve a CR or PR at EOI will receive post-induction treatment (referred to as maintenance) with Atezo-G.

During the safety run-in phase, the patients within each treatment group will be closely monitored for adverse events during an observation window, defined as Cycles 2 and 3 of induction treatment (the first two treatment cycles that contain atezolizumab), to determine if any of the stopping criteria have been met. Patients who discontinue from the study prior to completing Cycle 3 for reasons other than toxicity will be replaced.

Number of Patients

Up to 46 patients with FL will be enrolled in the Atezo-G-benda treatment group: 6 patients with previously untreated, or relapsed or refractory FL enrolled in the safety run-in phase and 34–40 patients with previously untreated FL enrolled in the expansion phase (depending on the number of patients needed to achieve a total enrollment of 40 patients with previously untreated FL). A total of 7 patients with previously untreated, or relapsed or refractory FL were enrolled in the Atezo-G-CHOP treatment group during the safety run-in phase. Per current amendment, , further enrollment in the Atezo-G-CHOP treatment group is stopped. A total of 40 patients with previously untreated DLBCL will be enrolled in the Atezo-R-CHOP treatment group. Therefore, enrollment of up to 92 patients is planned for this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- For patients enrolled in the safety run-in phase: lymphoma classified as either of the following:

  Relapsed or refractory FL after treatment with at least one prior chemoimmunotherapy regimen

  Previously untreated Grade 1, 2, or 3a FL that requires treatment, defined as meeting at least one of the Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria, as listed below:

  Bulky disease, defined as a nodal or extranodal (except spleen) mass ≥ 7 cm in the greatest diameter

  Local symptoms or compromise of normal organ function due to progressive nodal disease or extranodal tumor mass

  Presence of B symptoms

  Presence of symptomatic extranodal disease (e.g., pleural effusions, peritoneal ascites)

  Cytopenias due to underlying lymphoma (i.e., ANC $< 1.0 \times 10^9$/L, hemoglobin < 10 g/dL, and/or platelet count $< 100 \times 10^9$/L)

  Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
- For patients enrolled in the expansion phase: lymphoma classified as either of the following:

  Previously untreated Grade 1, 2, or 3a FL that requires treatment, defined as meeting at least one of the GELF criteria (listed above)

  Previously untreated advanced DLBCL, defined as Stage III or IV with an International Prognostic Index (IPI) ≥ 2 or Stage II with bulky disease (defined as at least one lesion ≥ 7 cm)
- Histologically documented CD20-positive lymphoma
- Fluorodeoxyglucose-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)
- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL

  For patients with FL, if the available biopsy was not done within 12 months, a repeat biopsy is strongly recommended.
- For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 18 months after the last dose of study treatment for patients in the Atezo-G-benda and Atezo-G-CHOP treatment groups or for at least 12 months after the last dose of study treatment for patients in the Atezo-R-CHOP treatment group.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

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

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or 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 3 months after the last dose of study treatment. Men must refrain from donating sperm for the same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study treatment.

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

Exclusion Criteria

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

- Histological evidence of transformation of FL into high-grade B-cell non-Hodgkin's lymphoma
- Central nervous system lymphoma or leptomeningeal infiltration
- For patients with DLBCL: preplanned consolidative radiotherapy
- 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, 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.
- For patients with relapsed or refractory FL (enrolled in the safety run-in phase)

  Prior allogeneic or autologous stem cell transplantation

  Prior anthracycline therapy (in patients enrolled in the Atezo-G-CHOP treatment group)

  Treatment with fludarabine or alemtuzumab within 12 months prior to Day 1 of Cycle1

  Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA4, anti–programmed death–1, and anti– programmed death–ligand 1 therapeutic antibodies

  Treatment with a monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate 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

  Clinically significant toxicity (other than alopecia) from prior treatment that has not resolved to Grade ≤ 2 (per National Cancer Institute Common Terminology Criteria in Adverse Events v4.0) prior to Day 1 of Cycle 1
- History of solid organ transplantation
- History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies
- Known sensitivity or allergy to murine products

- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab, obinutuzumab, rituximab, or bendamustine formulation, including mannitol
- 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 intravenous (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.
- Positive for hepatitis B surface antigen, total hepatitis B core antibody, or hepatitis C virus 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 progressive multifocal leukoencephalopathy
- Vaccination with a live virus vaccine within 28 days prior to Day 1 of Cycle 1
- 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.
- 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 Day 1, or anticipation of a major surgical procedure during the course of the study
- For patients who will be receiving CHOP: left ventricular ejection fraction $< 50\%$ by multiple-gated acquisition scan or echocardiogram
- 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

- 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)

  AST or ALT $> 2.5 \times$ ULN

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

  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 who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to Day 1 of Cycle 1.

- 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 FL patients have completed or discontinued study treatment and all enrolled DLBCL patients have been followed for at least 1 year after they have completed or discontinued study treatment.

Length of Study

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

Investigational Medicinal Products

Obinutuzumab will be administered 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 cycle (i.e., every 2 months) during maintenance treatment (eligible patients with FL only). No dose modification for obinutuzumab is allowed.

Atezolizumab will be administered at a flat dose consisting of one of the following: a) 1200 mg every 3 weeks (1200 mg on Day 1 of Cycles 2 and beyond, given in 21-day cycles either with G-CHOP as induction treatment or alone as consolidation treatment); b) 840 mg every 2 weeks (840 mg on Days 1 and 15 of Cycles 2–6, given in 28-day cycles with G-benda as induction treatment); or c) 1680 mg every 4 weeks (840 mg on Days 1 and 2 of each month, given with obinutuzumab as maintenance treatment). . No dose modification for atezolizumab is allowed.

Bendamustine will be administered by IV infusion at a dose of 90 mg/m^2 on Days 1 and 2 of each 28-day cycle, for up to 6 cycles. There must be a minimum of 12 hours between each bendamustine administration.

Rituximab will be administered by IV infusion at the dose of 375 mg/m^2 on Day 1 of Cycles 1−8. No dose modification for rituximab is allowed.

Non-Investigational Medicinal Products

CHOP agents will be administered at the standard dose and schedule, according to the standard preparation and infusion procedures of each investigational site. The CHOP regimen consists of cyclophosphamide 750 mg/m^2 IV on Day 1, doxorubicin 50 mg/m^2 IV on Day 1, vincristine 1.4 mg/m^2 (maximum, 2 mg) IV on Day 1, and prednisone 40 mg/m^2 by mouth on Days 1–5.

Statistical Methods

Primary Analysis

The primary and secondary efficacy analyses will be performed by treatment group, with patients grouped according to treatment received. For the Atezo-R-CHOP treatment group, the efficacy analyses will include all patients enrolled in the expansion phase. For the Atezo-G-benda treatment group, the efficacy analyses will include all patients enrolled in the expansion phase as well as patients with previously untreated FL who were enrolled in the safety run-in phase.

Response will be determined through use of the modified Cheson 2007 criteria, which take into account both PET-CT and CT scan results, and through use of the PET-CT–based Lugano 2014 criteria.

Determination of Sample Size

Data from completed and ongoing studies in similar disease settings will be used as historical controls for comparison. Currently available data indicate that the historical CR rate is approximately 40% for first-line treatment of FL and 59% for first-line treatment of DLBCL, as assessed by Cheson 2007 criteria. A sample size of 40 patients is deemed sufficient to provide adequate precision for the point estimate and for the lower bound of the two-sided 90% CI to rule out a clinically uninteresting probability of response of $<$40% in FL and $<$ 59% in DLBCL, assuming an observed PET-CT–defined CR rate of 55% and 72%, respectively. Updated estimates of the proportion of patients expected to achieve a PET-CT–defined CR for each histological subtype are expected to be available from ongoing studies by the time of the first interim analysis and will be used as reference data.

Interim Analyses

It is anticipated that at least one interim analysis will be conducted during the expansion phase of the study, when at least 15 patients have been evaluated for PET-CT-defined CR at the EOI. Additional analyses may be conducted to guide early stopping of enrollment for safety on the basis of observed toxicities and the ability to maintain chemotherapy dose intensity.

During the expansion phase, a modified version of the predictive probability design may be used to guide early stopping for futility by comparing the observed proportion of patients who achieve a PET-CT–defined CR at EOI in each expansion cohort with that in historical controls. The earliest interim analysis would occur after at least 15 patients have been evaluated for PET-CT–defined CR at EOI.

If, at any time, an interim analysis suggests that the proportion of patients achieving a PET-CT–defined CR for one of the expansion cohorts is lower or higher than expected, the Internal Monitoring Committee (IMC) will review the data and decide whether to recommend an early decision to stop enrollment in that subgroup. Interim analysis decision rules will be based on the modified version of the predictive probability that the trial will have a positive outcome if carried out to completion and will use the historical control data available at the time of analysis.

Additional 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 document.

LIST OF ABBREVIATIONS AND OF TERMS

Abbreviation	Definition
^{18}F-FDG	^{18}F-fluorodeoxyglucose
ABC	activated B cell–like (subgroup)
ADR	adverse drug reaction
ALP	alkaline phosphatase
ATA	anti-therapeutic antibody
Atezo-G	atezolizumab plus obinutuzumab
Atezo-G-benda	atezolizumab in combination with obinutuzumab plus bendamustine
Atezo-G-CHOP	atezolizumab in combination with obinutuzumab plus CHOP
Atezo-R-CHOP	atezolizumab in combination with rituximab plus CHOP
BSA	body surface area
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CLL	chronic lymphocytic leukemia
CR	complete response
CSR	clinical study report
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	trough concentration
CVP	cyclophosphamide, vincristine, and prednisone
CYP	cytochrome P450
DFS	disease-free survival
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
FcγRIII	Fc gamma receptor type III
FDG	fluorodeoxyglucose
FL	follicular lymphoma
FLIPI, FLIPI2	Follicular Lymphoma International Prognostic Index Follicular Lymphoma International Prognostic Index 2

Abbreviation	Definition
G	obinutuzumab (GA101)
G-benda	obinutuzumab plus bendamustine
GCB	germinal-center B cell–like (subgroup)
G-CHOP	obinutuzumab plus CHOP
GClb	G-chlorambucil
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
G-CVP	obinutuzumab plus cyclophosphamide, vincristine, and prednisone
GELF	Groupe d'Etudes des Lymphomes Folliculaires
GI	gastrointestinal
HACA	human anti-chimeric antibodies
HAHA	human anti-human antibody
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IC	immune cell
ICH	International Conference on Harmonisation
IFN-α	interferon alpha
IFN-γ	interferon gamma
Ig	immunoglobulin
IL	interleukin
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug
iNHL	indolent non-Hodgkin's lymphoma
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous
IxRS	interactive voice or web-based response system
JC	John Cunningham

Abbreviation	Definition
LFT	liver function test
LMWH	low-molecular-weight heparin
Lugano 2014 criteria	Lugano Response Criteria for Malignant Lymphoma
LVEF	left ventricular ejection fraction
modified Cheson 2007 criteria	modified version of the Revised Response Criteria for Malignant Lymphoma
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria in Adverse Events
NHL	non-Hodgkin's lymphoma
NK	natural killer
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	by mouth
PR	partial response
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
R	rituximab
RANKL	Receptor activator of nuclear factor kappa-B ligand
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RP2D	recommended Phase II dose
R-CHOP	rituximab plus CHOP chemotherapy
RClb	R-chlorambucil
SCT	stem cell transplantation

Abbreviation	Definition
Teffs	effector T cells
TEN	toxic epidermal necrolysis
TFH	helper T cell
TIL	tumor-infiltrating lymphocyte
TLS	tumor lysis syndrome
TP53	tumor protein p53
TSH	thyroid stimulating hormone
UBC	urothelial bladder cancer
UC	urothelial cancer
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). NHL is most often of B-cell origin, including a wide range of different subtypes of B-cell NHL, broadly divided into indolent and aggressive lymphomas, each with unique characteristics.

1.1.1 Follicular Lymphoma

Indolent NHLs (iNHLs) 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 iNHL, accounting for about 22% of all newly diagnosed cases of NHL (Armitage and Weisenburger 1998). Approximately 90% of the cases have a t(14;18) translocation, which juxtaposes BCL2 gene with the IgH locus and results in deregulated expression of BCL2.

FL remains an incurable disease with the currently available therapies. The addition of rituximab, an anti-CD20 monoclonal antibody, to commonly used induction chemotherapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); fludarabine; or bendamustine (Zelenetz et al. 2013; Dreyling et al. 2014), followed by rituximab maintenance therapy led to prolonged response 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 R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), for newly diagnosed DLBCL led to a significant improvement in survival in patients of all age groups. In older patients (>60 years), 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 plus ifosfamide, carboplatin, and etoposide or rituximab plus dexamethasone, cytosine arabinoside, and cisplatin followed by autologous stem cell transplantation (SCT). Approximately half of the patients do not achieve a complete response 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 tumor protein p53 (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). 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% versus 72%) (Savage et al. 2009). Concurrent MYC and IGH-BCL2 rearrangement ("double-hit" DLBCL), observed in 2%–11% of DLBCL patients, 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 predictor of poor overall survival (OS) (Xu-Monette et al. 2012; Young et al. 2008).

DLBCL remains a high unmet medical need for which novel targeted therapies are needed to move the field beyond R-CHOP.

1.2 BACKGROUND ON OBINUTUZUMAB

Obinutuzumab (also known as GA101) 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 Fc gamma receptors type III (FcγRIII) 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.

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) as well as 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 promising anti-tumor activity of obinutuzumab (Mössner et al. 2010; Dalle et al. 2011) and superiority of obinutuzumab over rituximab (Herting et al. 2014).

For more detailed nonclinical information on obinutuzumab, please refer to the current version of the obinutuzumab Investigator's Brochure.

1.2.2 Clinical Studies with Obinutuzumab

Obinutuzumab is being studied in patients with CLL, iNHL, NHL, DLBCL, B-cell lymphoma 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, please refer to the obinutuzumab Investigator's Brochure.

1.2.2.1 Summary of Clinical Efficacy of Obinutuzumab in Patients with NHL

In studies of obinutuzumab monotherapy in patients with relapsed or refractory NHL (Studies BO20999, BO21003, 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, bendamustine) in patients with previously untreated, or relapsed or refractory NHL (BO21000 and GAO4915g), the proportion of patients with a CR or PR at the end of induction (EOI) treatment ranged from 82% to 96%. The CR rate was higher with combination therapy (35%–39% in previously untreated FL, 39%–50% in relapsed or refractory FL, and 55% in previously untreated DLBCL) than with monotherapy.

A Phase III study, GAO4753g, investigated obinutuzumab plus bendamustine (G-benda) compared with bendamustine alone in patients with rituximab-refractory iNHL (n = 396). Patients in the G-benda treatment group who had not experienced disease progression at the EOI received obinutuzumab monotherapy every 2 months for up to 2 years. On the basis of positive results from this study that demonstrated significant improvement in PFS in the GB treatment group, with a median 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 or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen (see Section 1.2).

A Phase III study, BO21223, investigated obinutuzumab plus chemotherapy (G-benda, obinutuzumab plus CVP [G-CVP], G-CHOP) compared with rituximab plus chemotherapy in patients with previously untreated iNHL (FL cohort, n = 1202). On the basis of positive results that demonstrated significant improvement in PFS in the obinutuzumab-chemotherapy arm, the Independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor at a pre-planned interim analysis. Obinutuzumab was granted approval for use in patients with previously untreated FL in European Union, United States, and elsewhere.

A Phase III study, BO21005, investigated obinutuzumab plus CHOP (G-CHOP) compared with rituximab plus CHOP (R-CHOP) in patients with previously untreated DLBCL. The study did not meet its primary endpoint of PFS at final analysis.

1.2.2.2 Summary of Clinical Safety of Obinutuzumab

As of 31 October 2017, 4981 patients have received obinutuzumab via clinical trial participation. Patients with NHL (including DLBCL, iNHL, and CLL) have been treated with obinutuzumab given as monotherapy or in combination with CHOP, bendamustine, fludarabine plus cyclophosphamide, or chlorambucil, at doses ranging from 50 to 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 versus 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. In the CLL population, the incidence ranged from 66% in previously untreated patients receiving obinutuzumab plus chlorambucil (Study BO21004) to 100% in relapsed or refractory patients receiving obinutuzumab monotherapy (pooled data from

Studies BO21003 and BO20999, CLL cohorts). Anaphylaxis has also been reported in patients treated with obinutuzumab.

In the NHL population, the incidence of IRRs in studies of obinutuzumab monotherapy was 73%–75% (pooled data from Study BO21003 and from high-dose, NHL cohorts from Study BO20999). In studies of obinutuzumab in combination with either CHOP (Study GAO4915g) or bendamustine (Study BO21000), the incidence of IRRs considered to be related to obinutuzumab was 56%–59%.

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

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets programmed death–ligand 1 (PD-L1) and inhibits its interaction with its receptors, programmed death–1 (PD-1) and B7-1 (also known as CD80). Both of these interactions are reported to provide inhibitory signals to T cells. Therapeutic blockade 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 use in patients with metastatic non–small cell lung cancer that has relapsed after or is refractory to platinum-based chemotherapy. Atezolizumab is being investigated as a potential treatment against 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, including providing 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.

The combination of a surrogate anti-mouse PD-L1 antibody with an anti-mouse CD20-depleting antibody has been tested using a syngeneic A20 lymphoma model in immune-competent mice. Results from this nonclinical 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 (Genentech data).

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

1.3.2 Clinical Studies with Atezolizumab

Atezolizumab has been tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies; Phase I, II and III studies are also on-going in multiple indications. 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, 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 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 to 20 mg/kg across multiple tumor types. No dose-limiting toxicities (DLTs) have been observed at any dose level, and no maximum tolerated dose (MTD) has been established. In Study GP28328, a Phase Ib multi-arm study, patients with solid tumors were treated with atezolizumab 1200 mg q3w or 840 mg every 2 weeks (q2w) in combination with commonly used chemotherapies (i.e., oxaliplatin, leucovorin, and 5-fluorouracil; carboplatin; paclitaxel; pemetrexed; nanoparticle albumin-bound paclitaxel) and/or bevacizumab (biologic agent) at standard doses. Preliminary data available for 144 patients show a manageable

safety profile without exacerbation of chemotherapy- or bevacizumab-associated adverse events.

Summary of Adverse Events

Adverse events were reported in 619 of the 629 (98.4%) safety-evaluable patients. 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 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%) as the most frequently occurring events (≥ 0.8% or ≥ 5 patients).

Serious adverse events have been reported in 261 of 629 (41.5%) patients in Study PCD4989g. Reported serious adverse events were consistent with the underlying disease. Treatment-related serious adverse events were reported in 9.1% of patients. Atezolizumab-related serious adverse events 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 3 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 hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myocarditis, and hypophysitis.

Guidelines for the management of potential immune-related adverse events are described in Section 5.1.7.

Refer to the Atezolizumab Investigator's Brochure for details on adverse events observed in patients treated with atezolizumab.

1.3.2.2 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 in baseline tumor tissue were also conducted.

Efficacy results, based on a data cutoff date of 15 December 2015, are summarized below for the NSCLC, RCC, and UBC cohorts. See the Atezolizumab Investigator's Brochure for clinical activity in combination studies and for additional details.

Patients with Hematologic Malignancies

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. A Phase Ib study (GO29383) of atezolizumab 1200 mg q3w in combination with obinutuzumab was performed in patients with relapsed or refractory FL and DLBCL (see Section 1.4.3)

Please refer to the Atezolizumab Investigator's Brochure for details on clinical activity in patients treated to date.

1.4 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).

1.4.1 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. 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 blockade 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 1.4.2). 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). Consistent with published data, 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).

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

Pidilizumab (CT-011), a humanized IgG-1k monoclonal antibody that targets PD-1, has been tested in Phase I and II clinical studies in hematological 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, 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, positive correlation with PFS was observed for a T-cell activation signature created by gene expression profile studies. 41 genes have been identified to be more highly expressed in Teffs as compared with follicular helper T cells (TFH). Low expression of this signature, suggesting more TFH and fewer PD-1+ Teffs within the tumor, predicted less tumor shrinkage and shorter PFS: median of 12.7 months (95% CI: 6.5, 21.6) for signature-low patients versus not reached (95% CI: NA, NA) for signature-high patients (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 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 overall 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 is the first-in-class PD-L1 inhibitor being tested in lymphoma. Eleven patients with refractory or relapsed hematologic malignancies have been treated with atezolizumab in Study PCD4989g, including 7 patients with lymphoma (see Section 1.3.2.2). Among the 10 patients who were evaluable for response, the best response was PR for the 2 patients with cutaneous T-cell lymphoma and stable disease for the 3 patients with FL and the 1 patient with Hodgkin's lymphoma, and 2 patients with multiple myeloma.

A Phase Ib study (GO29383) of atezolizumab 1200 mg q3w in combination with obinutuzumab was performed in patients with relapsed or refractory FL and DLBCL (see Section 1.4.3).

1.4.3 Rationale for Treatment Combination

Prior to the implementation of Protocol Version 3, patients with DLBCL enrolled in the expansion phase were to receive Atezo-G-CHOP. However, results from Study BO21005 demonstrated that G-CHOP did not improve PFS compared with the standard R-CHOP regimen in patients with previously untreated DLBCL. Thus, with the implementation of Protocol Version 3, patients with DLBCL enrolled in the expansion phase will receive atezolizumab in combination with R-CHOP.

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 obinutuzumab and rituximab induce direct tumor-cell killing with subsequent release of tumor antigens for immune presentation (immunogenic cell death). Additionally, obinutuzumab was engineered to augment antibody-dependent cellular cytotoxicity, resulting in enhanced binding to FcγRIIIa (CD16). Thus, obinutuzumab has the ability to enhance T-cell priming and IC activation through interactions with dendritic cells and NK cells carrying FcγRIIIa. Atezolizumab affects primarily the effector phase of the immune response, by restoring cytotoxic T-cell function.

Studies of obinutuzumab plus atezolizumab or rituximab plus atezolizumab have not been performed in nonclinical mouse 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 (see Section 1.3.1). Although the anti-CD20 agent used in this study is not completely identical to obinutuzumab, the study results provide compelling proof of concept for exploring these combinations in clinical trials.

Clinical data for G-benda or G-CHOP in B-cell NHL are available from a Phase Ib/II study in patients with previously untreated and relapsed or refractory FL (Study BO21000). In this study, 81 patients with previously untreated FL received induction therapy with G-benda (n = 41) or G-CHOP (n = 40), resulting in a CR rate at EOI of 37% and 35%, respectively (Dyer et al. 2012). Both combinations had a manageable safety profile, with neutropenia reported as the most common Grade ≥ 3 adverse event during induction treatment, occurring in 29% of patients in the G-benda arm and 43% of patients in the G-CHOP arm. Grade ≥ 3 infections occurred in 10% of patients receiving G-benda and 23% of patients receiving G-CHOP. All events resolved with appropriate management. Seventy-two responders at EOI, including 36 patients in the G-benda treatment group and 36 patients in the G-CHOP treatment group, received maintenance with obinutuzumab administered every 3 months for up to 2 years. The CR rate at the end of treatment was 61% and 70% in the G-benda and G-CHOP treatment groups, respectively (Dyer et al. 2014). Maintenance treatment with obinutuzumab was generally well tolerated. Clinically relevant neutropenia was reported in 14% of patients in the G-benda treatment group but was not observed in the G-CHOP treatment group. Grade ≥ 3 infections occurred in 17% of patients in the G-benda treatment group and 14% of patients in the G-CHOP treatment group. Median IgG, IgA, and IgM levels remained within the normal range during maintenance. In the relapsed or refractory cohort of this study, 28 patients received induction therapy with G-CHOP, resulting in a CR rate at EOI of 39%. Neutropenia was the most common Grade ≥ 3 adverse event occurring in 43% of patients (Radford et al. 2013).

G-CHOP was evaluated in a Phase Ib/II study in 100 patients with previously untreated DLBCL (Study GAO4915g). Data from this study demonstrate encouraging efficacy, with a CR rate of 55% per investigator review and 58% per centralized review (Zelenetz et al. 2013; GAO4915g clinical study report [CSR]), and a manageable safety profile. Neutropenia was the most common Grade ≥ 3 adverse event, occurring in 42% of patients. Grade ≥ 3 infections were reported in 21% of patients. However, these could be addressed by prophylactic administration of granulocyte colony-stimulating factor (G-CSF) support. As consistently demonstrated across randomized trials investigating obinutuzumab chemotherapy versus rituximab chemotherapy in patients with B-cell malignancies, the safety profile of rituximab chemotherapy tended to compare favorably with the safety profile of obinutuzumab chemotherapy. Results from the Phase III study (BO21005 [GOYA]) of G-CHOP versus R-CHOP in patients with previously untreated DLBCL are supporting the favorable safety profile of R-CHOP when compared with G-CHOP (see Table 11). Results from the Phase III study (BO21223 [GALLIUM]) of obinutuzumab chemotherapy (G-benda, G-CVP, G-CHOP) versus rituximab chemotherapy, followed by maintenance, as first-line treatment in patients with previously untreated iNHL (FL cohort, n = 1202) demonstrated a higher frequency of Grade 3–5 adverse events (74.6%) and serious adverse events (46.1%) in patients treated with obinutuzumab chemotherapy compared with those treated with rituximab chemotherapy (67.8% and 39.9%, respectively). When comparing safety profile by

chemotherapy treatment group in this study, higher incidence of Grade 3–5 adverse events and serious adverse events was observed in the G-CHOP treatment group (88.5% and 39.9%, respectively) compared with the R-CHOP treatment group (75.2% and 31.5%, respectively) (see CSR 1067980).

Results from the Phase III Study BO21004 (Stage 2), comparing G-chlorambucil (GClb) with R-chlorambucil (RClb) in patients with previously untreated CLL (n = 663), indicated that patients exposed to GClb were at higher risk of IRR, TLS, thrombocytopenia, and neutropenia than patients exposed to RClb (Goede et al. 2014).

A Phase Ib study (GO29383) of atezolizumab in combination with obinutuzumab in patients with relapsed or refractory FL and DLBCL 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 is consistent with what has been observed with the respective single agents and manageable in the NHL setting. 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 NHL treated with atezolizumab + obinutuzumab. The efficacy data 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%, with a complete response rate of 26.1%. The median duration of response and median PFS at the time of clinical cutoff were 15.0 and 15.1 months, respectively. In patients with relapsed/refractory DLBCL, the end of induction assessment was 11.1% with one patient achieving CR at end of induction. The median duration of response and median PFS at the time of clinical cutoff were 3.5 and 2.7 months, respectively (Palomba et al. 2017).

Available data and current concepts of immunotherapy suggest that there is a strong rationale to expect an improved benefit-risk ratio with the addition of atezolizumab to G-benda and R-CHOP in FL and DLBCL, respectively. The expected benefit may result from the strengthened immunotherapy component of the combinations, able to lead to robust and long-lasting anti-tumor responses, along with a minimal risk of overlapping toxicities, expected to be manageable in the clinical setting (see Section 5.1.6).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of induction treatment consisting of atezolizumab in combination with obinutuzumab plus bendamustine (Atezo-G-benda) in patients with FL, atezolizumab in combination with obinutuzumab plus CHOP (Atezo-G-CHOP) in patients with FL, and atezolizumab in combination with rituximab plus CHOP (Atezo-R-CHOP) in patients with DLBCL, followed by post-induction treatment consisting of either atezolizumab plus obinutuzumab (Atezo-G) in patients with FL who achieve a CR or PR at EOI or atezolizumab alone in patients with DLBCL who achieve a CR at EOI (see Section 3.1 for details). 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.

2.1 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety and tolerability of induction treatment with either Atezo-G-benda or Atezo-G-CHOP in patients with FL, Atezo-R-CHOP in patients with DLBCL, and post-induction treatment with either Atezo-G in patients with FL or atezolizumab alone in patients with DLBCL on the basis of the following endpoints:

- Nature, frequency, severity, and timing of adverse events (see Section 3.1.1)
- Changes in vital signs, ECGs, and clinical laboratory results during and following study treatment administration

2.2 EFFICACY OBJECTIVES

Response will be determined through use of the PET-CT–based Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014; see Appendix 7), hereinafter referred to as Lugano 2014 criteria. Response will also be determined through use of the modified version of the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007; see Appendix 8), hereinafter referred to as modified Cheson 2007 criteria, which take into account both PET-CT and CT scan results. Response will be determined by an Independent Review Committee (IRC) and 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 either Atezo-G-benda or Atezo-R-CHOP, on the basis of the following endpoint:

- CR at EOI, as determined by the IRC using Lugano 2014 criteria

2.2.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of induction treatment with either Atezo-G-benda or Atezo-R-CHOP and post-induction treatment with either Atezo-G or atezolizumab alone, on the basis of the following endpoints:

- CR at EOI, as determined by the investigator using Lugano 2014 criteria
- CR at EOI, as determined by the IRC and by the investigator using modified Cheson 2007 criteria
- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator using Lugano 2014 criteria and modified Cheson 2007 criteria
- Best response of CR or PR during the study, as determined by the investigator using modified Cheson 2007 criteria

2.2.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of induction treatment with either Atezo-G-benda or Atezo-R-CHOP and post-induction treatment with either Atezo-G or atezolizumab alone, on the basis of the following endpoints:

- For patients who have positive PET scans at EOI: CR at 12 months, as determined by the IRC and by the investigator using Lugano 2014 criteria
- CR at 12, 24, and 30 months in patients with previously untreated FL, as determined by the investigator using modified Cheson 2007 criteria
- PFS, defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by the investigator using modified Cheson 2007 criteria, or death from any cause
- EFS, defined as the time from initiation of study treatment to any treatment failure, including disease progression or relapse, as determined by the investigator using modified Cheson 2007 criteria, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first
- Disease-free survival (DFS), defined, among patients achieving a CR, as the time from the first occurrence of a documented CR to relapse, as determined by the investigator using modified Cheson 2007 criteria, or death from any cause, whichever occurs first
- OS, defined as the time from initiation of study treatment to death from any cause

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objectives for this study are to characterize the pharmacokinetics of atezolizumab, rituximab, and obinutuzumab when administered as induction treatment consisting of either Atezo-G-benda, Atezo-G-CHOP, or Atezo-R-CHOP or post-induction treatment consisting of either Atezo-G or atezolizumab alone, on the basis of the following endpoints:

- Observed serum obinutuzumab concentration at specified timepoints

- Observed serum atezolizumab concentration at specified timepoints
- Observed serum rituximab concentration at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab, to rituximab, and to atezolizumab 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 anti-therapeutic antibodies (ATAs) to atezolizumab 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:

- Correlation between non-inherited biomarkers (listed in Section 4.5.6) and efficacy, safety, PK, or immunogenicity endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study

This Phase Ib/II, open-label, multicenter, non-randomized study will evaluate the safety, efficacy, and pharmacokinetics of combination treatment with atezolizumab, obinutuzumab, and chemotherapy in patients with FL and atezolizumab, rituximab, and chemotherapy in patients with DLBCL.

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

During the safety run-in phase, 12 patients with previously untreated, or relapsed or refractory FL are to be enrolled in either the Atezo-G-benda treatment group (n = 6) or the Atezo-G-CHOP treatment group (n = 6) at the discretion of the investigator. Patients will receive 6 cycles (Cycles 1–6) of induction treatment with either Atezo-G-benda or Atezo-G-CHOP (with atezolizumab starting in Cycle 2 for both treatment groups), as outlined in Section 3.1.2. Patients who achieve a CR or PR at EOI will receive post--induction treatment (referred to as maintenance) with Atezo-G (see Section 3.1.2 for details).

During the safety run-in phase, the patients within each treatment group will be closely monitored for adverse events during an observation window, defined as Cycles 2 and 3 of induction treatment (the first two treatment cycles that contain atezolizumab), to determine if any of the stopping criteria (as defined below) have been met. Patients who discontinue from the study prior to completing Cycle 3 for reasons other than toxicity will be replaced.

Stopping Criteria

Stopping criteria will be used to determine whether the study will continue with patient enrollment into the expansion phase. Stopping criteria are defined as any one of the following events that occurs during Cycle 2 or 3:

- Study treatment–related death in at least 1 patient
- Any of the following toxicities occurring in at least 2 patients:

  Anaphylaxis, acute respiratory distress, or Grade 4 IRR

  Hematologic toxicity that is related to study treatment and consists of either of the following:

  Grade ≥ 3 hematologic adverse event that requires study treatment to be withheld for > 21 days for Atezo-G-benda treatment group and > 14 days for Atezo-G-CHOP treatment group

  Recurrent Grade 4 neutropenia with infection, despite G-CSF support and dose modifications

  Non-hematologic toxicity that consists of either of the following:

  Grade ≥ 3 non-hematologic adverse event that has a reasonable possibility of being related to study treatment and either is life threatening or requires study treatment to be withheld for > 21 days for Atezo-G-benda treatment group and > 14 days for Atezo–G–CHOP treatment group

  Development of an atezolizumab-related immune-related adverse event that is life threatening or requires atezolizumab to be withheld for > 42 days

  Note: The maximum allowed dose delay is 21 days for patients with FL and 14 days for patients with DLBCL (see Section 5.1.7 for more details). However, during the safety run-in phase, the dose delay associated with the stopping criteria will be

restricted to 14 days for FL patients enrolled in the Atezo-G-CHOP treatment group. This will allow for a meaningful assessment of dose density maintenance under the same dose delay restrictions (i.e., 14 days) that will apply to DLBCL patients enrolled in the expansion phase.

During the safety run-in phase, the Medical Monitor will review data on an ongoing basis. After 6 patients within a treatment group have either completed Cycle 3 or discontinued because of a toxicity, an Internal Monitoring Committee (IMC), as described in Section 3.1.3, and the Principal Investigator will perform a formal review of the cumulative data and will make appropriate recommendations for further management of the study (e.g., proceed with the expansion phase, re-evaluate study treatment dosing regimen).

If the stopping criteria (as defined above) are not met during Cycles 2 and 3 among patients receiving Atezo-G-benda during the safety run-in phase, approximately 34–40 patients with previously untreated FL will be enrolled in the Atezo-G-benda treatment group, depending on the number of patients needed to achieve a total enrollment of 40 patients with previously untreated FL in this treatment group. Patients will receive 6 cycles (Cycles 1–6) of induction treatment with Atezo-G-benda (obinutuzumab and bendamustine for Cycles 1–6 and atezolizumab for Cycles 2–6), as outlined in Section 3.1.2. Patients who achieve a CR or PR at EOI will receive post-induction treatment (referred to as maintenance) with Atezo-G (see Section 3.1.2 for details).

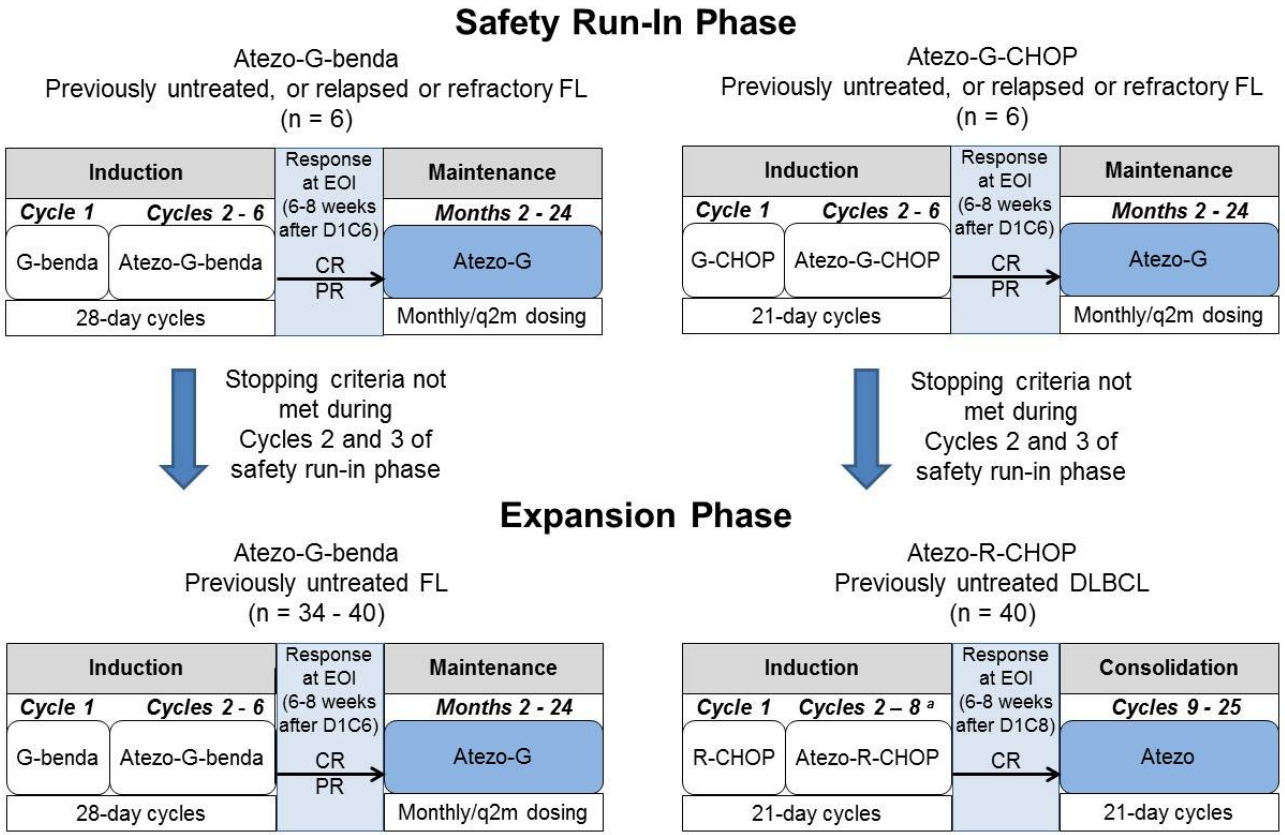
If the stopping criteria (as defined above) are not met during Cycles 2 and 3 among patients receiving Atezo-G-CHOP during the safety run-in phase, 40 patients with previously untreated DLBCL will be treated with Atezo-R-CHOP. Patients will receive 8 cycles (Cycles 1–8) of induction treatment with Atezo-R-CHOP (rituximab for Cycles 1–8, atezolizumab for Cycles 2–8, and CHOP for 6 or 8 cycles as determined by the investigator), as outlined in Section 3.1.2. Patients who achieve a CR at EOI will receive post-induction treatment (referred to as consolidation) with atezolizumab (see Section 3.1.2 for details).

Randomized clinical studies in patients with B-cell malignancies investigating obinutuzumab chemotherapy versus rituximab chemotherapy have consistently shown a more favorable safety profile of rituximab chemotherapy compared with obinutuzumab chemotherapy (see Section 1.4.3). For this reason, no safety run-in will be conducted in the Atezo-R-CHOP treatment group; the safety run-in results in the Atezo-G-CHOP treatment group are deemed sufficient to enroll patients in the Atezo-R-CHOP treatment group during expansion phase.

Patients enrolled in the expansion phase who discontinue from the study after Cycle 1 (i.e., prior to receiving atezolizumab) will be replaced.

A study schema is provided in Figure 1. Refer to Section 3.1.2 for details on the treatment regimens.

Figure 1 Study Schema



Atezo = atezolizumab; benda = bendamustine; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CR = complete response; D1C6 = Day 1 of Cycle 6; D1C8 = Day1 of Cycle 8; DLBCL = diffuse large B-cell lymphoma; EOI = end of induction; FL = follicular lymphoma; G = obinutuzumab; PR = partial response; q2m = every 2 months; R = rituximab.

[a] Patients with DLBCL will receive eight cycles (Cycles 1–8) of induction treatment with Atezo-R-CHOP (rituximab for Cycles 1–8, atezolizumab for Cycles 2–8, and six or eight cycles of CHOP as determined by the investigator).

Overall, it is planned to have 86–92 patients enrolled in this study, at approximately 20 investigative sites around the world.

All patients will be closely monitored for adverse events throughout the study and for at least 90 days after the last dose of study treatment (see Section 5.3.1). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria in Adverse Events, Version 4.0 (NCI CTCAE v4.0).

To characterize the PK properties of atezolizumab, obinutuzumab and rituximab, blood samples will be taken at various timepoints before and during dosing (see Appendix 4, Appendix 5, and Appendix 6).

Response will be determined by the IRC (see Section 3.1.4) and the investigator using the Lugano 2014 criteria (see Appendix 7) and the modified Cheson 2007 criteria (see Appendix 8). The primary efficacy endpoint will be based on IRC assessment of response through use of the Lugano 2014 criteria. Refer to Section 4.5.5 for details on tumor assessments.

Schedules of assessments are provided in Appendix 1, Appendix 2, and Appendix 3.

3.1.2 Treatment Regimens

All patients (safety run-in phase and expansion phase) will receive induction treatment, administered as outlined in Table 1.

Table 1 Induction Treatment

	Atezo-G-benda (FL) (28-day cycles) Safety Run-In and Expansion Phases	Atezo-G-CHOP (FL) (21-day cycles) Safety Run-In Phase	Atezo-R-CHOP (DLBCL) (21-day cycles) Expansion Phase
Cycle 1	• **Obinutuzumab** 1000 mg IV on Days 1, 8, and 15 • **Bendamustine** 90 mg/m^2 IV on Days 1 and 2	• **Obinutuzumab** 1000 mg IV on Days 1, 8, and 15 • **CHOP:** – Cyclophosphamide 750 mg/m^2 IV on Day 1 – Doxorubicin 50 mg/m^2 IV on Day 1 – Vincristine 1.4 mg/m^2 (max. 2 mg) IV on Day 1 – Prednisone [a] 40 mg/m^2 PO on Days 1–5	• **Rituximab** 375 mg/m^2 IV on Day 1 • **CHOP:** – Cyclophosphamide 750 mg/m^2 IV on Day 1 – Doxorubicin 50 mg/m^2 IV on Day 1 – Vincristine 1.4 mg/m^2 (max. 2 mg) IV on Day 1 – Prednisone [a] 40 mg/m^2 PO on Days 1–5
Cycles 2–6/8 [b]	• **Obinutuzumab** 1000 mg IV on Day 1 • **Bendamustine** 90 mg/m^2 IV on Days 1 and 2 • **Atezolizumab** 840 mg IV on Days 1 and 15	• **Obinutuzumab** 1000 mg IV on Day 1 [b] • **CHOP** [b]**:** – Cyclophosphamide 750 mg/m^2 IV on Day 1 – Doxorubicin 50 mg/m^2 IV on Day 1 – Vincristine 1.4 mg/m^2 (max. 2 mg) IV on Day 1 – Prednisone [a] 40 mg/m^2 PO on Days 1–5 • **Atezolizumab** 1200 mg IV on Day 1 [b]	• **Rituximab** 375 mg/m^2 IV on Day 1 • **CHOP** [b]**:** – Cyclophosphamide 750 mg/m^2 IV on Day 1 – Doxorubicin 50 mg/m^2 IV on Day 1 – Vincristine 1.4 mg/m^2 (max. 2 mg) IV on Day 1 – Prednisone [a] 40 mg/m^2 PO on Days 1–5 • **Atezolizumab** 1200 mg IV on Day 1 [b]

Atezo=atezolizumab; benda=bendamustine; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; G=obinutuzumab; IV=intravenous; max.=maximum; PO= by mouth; R=rituximab.

[a] Prednisolone may be given if prednisone is unavailable. The 40 mg/m^2 dose of prednisone on Day 1 will be replaced by oral corticosteroids given as premedication on Day 1 of Cycle 1 (and subsequent cycles as indicated) (see details on premedication in Section 4.3.2.9).

[b] All patients treated with Atezo-G-benda and Atezo-G-CHOP during the safety run-in phase (i.e., patients with FL) will receive induction treatment for 6 cycles. Patients treated with Atezo-R-CHOP during the expansion phase (i.e., patients with DLBCL) will receive eight cycles (Cycles 1–8) of induction treatment with Atezo-R-CHOP (rituximab for Cycles 1–8, atezolizumab for Cycles 2–8, and six or eight cycles of CHOP as determined by the investigator).

Patients with DLBCL who achieve a CR at EOI will receive post-induction treatment (referred to as consolidation) with atezolizumab, and patients with FL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as maintenance) with Atezo-G, as outlined in Table 2. Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity for up to 1 year for consolidation treatment or 2 years for maintenance treatment.

Table 2 Post-Induction Treatment

Patients with DLBCL	Consolidation treatment consisting of the following, administered in 21-day cycles for 17 cycles: • **Atezolizumab** 1200 mg IV on Day 1 of Cycles 9 to 25
Patients with FL	Maintenance treatment consisting of the following, administered for 24 months (from Month 1 to Month 24): • **Atezolizumab** 840 mg IV on Days 1 and 2 of each month, starting with Month 1 • **Obinutuzumab** 1000 mg IV on Day 1 of every other month (i.e., every 2 months), starting with Month 1

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

3.1.3 Internal Monitoring Committee

An IMC will monitor patient safety throughout the study. The IMC will include Sponsor's representatives from Clinical Science, Clinical Drug Safety and Biostatistics, independent of the study. In addition to the ongoing assessment of the incidence and nature of adverse events (particularly Grade ≥3 events), serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. Significant attention will be focused on the maintenance of dose intensity of chemotherapy in DLBCL. 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. *At the time when all patients have completed/discontinued study treatment (maintenance/consolidation), regular IMC assessments will no longer take place. Ad hoc meetings may be 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, and members' roles and responsibilities will be detailed in an IMC Charter.

3.1.4 Independent Review Committee

An IRC will assess all patients for response on the basis of imaging results, bone marrow biopsy results, and relevant clinical data. The review will consist of two parts:

a radiology review and an oncology review. The IRC will consist of radiologists, nuclear medicine experts, and a board-certified oncologist with experience in malignant lymphoma. Specific methodological and operational details will be specified in the IRC charter.

3.1.5 Post-Treatment Follow-Up and Survival Follow-Up

Patients who complete treatment or discontinue treatment for reasons other than disease progression will undergo assessments every 3 months during the post-treatment follow-up period, which will continue until disease progression, the start of new anti-lymphoma treatment, or the end of the study (as defined below), whichever occurs first. Patients who experience disease progression will undergo limited assessments every 3 months during the survival follow-up period, which will continue until the end of the study.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the time when all enrolled FL patients have completed or discontinued study treatment and all enrolled DLBCL patients have been followed for at least 1 year after they have completed or discontinued 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 1.1.1, despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, FL remains essentially an incurable disease for which more effective treatments are needed. G-benda has been shown to be effective and well tolerated in patients with previously untreated FL (see Section 1.4.3). Based on a preclinical and clinical rationale presented in Section 1.4.1 and Section 1.4.2, atezolizumab is expected to be active in FL and to provide an improved immunochemotherapy regimen when combined with G-benda. The risk of overlapping toxicities associated with combining atezolizumab with G-benda is expected to be minimal, and any such toxicities are expected to be manageable in the clinical setting (see Section 5.1.6). The expected benefit and minimal risk provide a rationale for testing Atezo-G-benda as first-line treatment in patients with FL. However, the combination will first be investigated in a safety run-in phase in which patients with relapsed or refractory FL can also be enrolled.

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. More effective treatments are needed for these patients. On the basis of a compelling biologic and clinical rationale, as presented in Section 1.4, the combination of atezolizumab with R-CHOP is a promising approach to expand the number of patients with DLBCL who achieve a cure. For ethical reasons related to the curative potential of

chemoimmunotherapy as first-line treatment for DLBCL, the Atezo-G-CHOP regimen will first be investigated in a safety run-in phase in which 6 patients with previously untreated, or relapsed or refractory FL will be enrolled.

The risk of overlapping toxicities associated with the addition of atezolizumab to R-CHOP is expected to be minimal. Additionally, preliminary data from the safety run-in phase prior to the implementation of Protocol Version 3 indicated that the combination of atezolizumab with G-CHOP was well tolerated. A total of 7 patients with FL (6 patients with previously untreated and 1 patient with relapsed or refractory disease) were enrolled and completed at least three cycles of induction treatment. None of the stopping criteria defined for the safety run-in phase of the study were met. There were no treatment-related Grade 3 and 4 adverse events during Cycles 2 and 3 (i.e., safety observation window). No treatment delays or treatment discontinuations due to adverse events were observed.

Consistently across randomized clinical trials in patients with B-cell malignancies investigating obinutuzumab chemotherapy versus rituximab chemotherapy, the safety profile of rituximab chemotherapy tended to compare favorably with the safety profile of obinutuzumab chemotherapy (see Section 1.4.3).

Thus, the expected benefit and acceptable risk provide the rationale for testing Atezo-R-CHOP as first-line treatment in patients with DLBCL. As presented in Section 3.1.3, patients will be monitored on a regular basis for safety, including the ability to maintain dose intensity of the CHOP chemotherapy.

3.3.2 Rationale for Dose and Schedule

3.3.2.1 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a flat dose consisting of one of the following: a) 1200 mg q3w (1200 mg on Day 1 of Cycles 2 and beyond, given in 21-day cycles either with G-CHOP as induction treatment or alone as consolidation treatment); b) 840 mg q2w (840 mg on Days 1 and 15 of Cycles 2–6, given in 28-day cycles with G-benda as induction treatment); or c) 1680 mg every 4 weeks (q4w) (840 mg on Days 1 and 2 of each month, given with obinutuzumab as maintenance treatment). All three 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 recommended Phase II dose (RP2D) 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 the 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: 1) 95%

tumor-receptor saturation is needed for efficacy and 2) 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 mg/kg to 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 in the dose-expansion stage. Anti-tumor activity has been observed across all dose cohorts. atezolizumab was safely administered to 11 patients with various hematologic malignancies (including 7 patients with lymphoma) at a dose of 15 mg/kg q3w (n = 1) and 20 mg/kg q3w (n = 10). There was no evidence of dose-dependent toxicity in this study. The MTD 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 lowest 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. 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. The combination has been safely administered in the first 3 patients who were evaluable for DLTs. Atezolizumab is added to obinutuzumab starting with Cycle 2, in an attempt to mitigate the risk of increased IRRs during the first infusion of obinutuzumab. The incidence and severity of IRRs related to obinutuzumab decrease substantially with the second and subsequent infusions.

For the q2w dosing interval, the fixed dose of 840 mg q2w is the equivalent of a weight-based dose of 15 mg/kg q3w. This dosing schedule is currently being evaluated in patients with advanced solid tumors in combination with chemotherapy or biologic agents (see Section 1.3.2.1).

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 area under the curve would be comparable to that of 1200 mg q3w (Genentech data). The

total dose of 1680 mg will be administered as 840 mg on Day 1 and Day 2 of a 28-day cycle. The total dose is split into two daily doses to minimize the risk of exceeding safe limits for manufacturing process–derived impurities such as host cell DNA and endotoxins. 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.

Consistent with the dosing schedule used in Study GO29383, in this study, atezolizumab will be added to G-benda and G-CHOP starting with Cycle 2.

3.3.2.2 Rationale for Obinutuzumab, Bendamustine, Rituximab, and CHOP Dose and Schedule

In two recent Phase III trials testing the combination of bendamustine and rituximab in previously untreated patients with iNHL (Rummel et al. 2013; Flinn et al. 2014), bendamustine was safely administered and active at a dose of 90 mg/m^2 on Days 1 and 2 of each 28 day-cycle. The dose of 90 mg/m^2 is also the dose of bendamustine recommended at a consensus conference of hematologists when used in combination with rituximab (Cheson et al. 2010).

G-benda was shown to be active and safe in 41 patients with previously untreated FL in Study BO21000 and in 2 Phase III studies in patients with previously untreated iNHL (Study BO21223) and rituximab-refractory iNHL (Study GAO4753g). In all three studies, treatment has been given in 28-day cycles. For induction therapy, obinutuzumab has been administered at a flat dose of 1000 mg on Days 1, 8, and 15 of Cycle 1 and on Day 1 of each subsequent cycle (Cycles 2–6), and bendamustine has been administered at a dose of 90 mg/m^2 on 2 consecutive days of each cycle. In patients achieving a CR or PR at EOI, obinutuzumab has been administered as maintenance therapy at a dose of 1000 mg every 2 months for 2 years. On the basis of available clinical data and to maintain consistency with the ongoing trials, the same obinutuzumab and bendamustine dosing regimens will be administered in this study.

G-CHOP was shown to be active and safe in 100 patients with previously untreated DLBCL in Study GAO4915g and in 40 patients with previously untreated FL in Study BO21000. G-CHOP has also been evaluated in Study BO21005, a Phase III study in patients with previously untreated DLBCL. In all three studies of G-CHOP, treatment is given in 21-day cycles, with obinutuzumab administered at a flat dose of 1000 mg on Days 1, 8, and 15 of Cycle 1 and on Day 1 of each subsequent cycle (Cycles 2–6 or 2–8) and CHOP administered at standard doses during each cycle. On the basis of clinical experience to date, and to maintain consistency with the ongoing trial, the same obinutuzumab and CHOP dosing regimens have been administered to patients with FL enrolled in the safety run-in phase.

R-CHOP is approved for treatment of DLBCL in the United States and in the European Union, as well as in many other countries and regions worldwide, on the basis of the results from three randomized, prospective studies of approximately 2000 previously untreated patients with advanced DLBCL (Coiffier et al 2002; Habermann et al. 2006; Pfreundschuh et al. 2006). On the basis of these studies, a dosing regimen of up to eight cycles of rituximab (375 mg/m^2 on Day 1 of each cycle) combined with six or eight cycles of CHOP is considered to be the standard of care for patients with advanced DLBCL (NCCN Guidelines® 2016) and will be used in this study.

3.3.2.3 Rationale for Treatment Duration

The objective of post-induction treatment is to improve the response to induction therapy, not only by converting a PR to a CR, but also by eradicating minimal residual disease (MRD) to achieve a molecular response in patients with a clinical CR after induction treatment, thus reducing the relapse risk for responders.

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). Final results from the maintenance phase of the Phase Ib study, BO21000, demonstrated that maintenance treatment with obinutuzumab monotherapy after obinutuzumab plus chemotherapy induction is active and generally well tolerated (Section 1.4.3). A Phase III study, BO21223, is currently investigating obinutuzumab versus rituximab as chemoimmunotherapy induction, followed by immunotherapy maintenance, in patients with untreated iNHL, including FL. Under the assumption that Study BO21223 will demonstrate greater clinical benefit with obinutuzumab- compared with rituximab-containing regimens, potentially altering the standard of care in FL, it appears important to investigate the combination of obinutuzumab with new targeted drugs in this setting. On the basis of a compelling nonclinical rationale (presented in Section 1.4.3), 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. Building on the obinutuzumab dosing schedule tested in the ongoing Phase III study (i.e., every 2 months for 2 years' duration), atezolizumab will be administered on a monthly basis for the same treatment period of 2 years.

Although most patients with DLBCL achieve complete metabolic response with first-line therapy, up to 40% ultimately relapse. Relapses most likely originate from MRD that is undetectable by radiologic examination. Although no therapy has been demonstrated to be effective in DLBCL after standard rituximab-based immunochemotherapy, PD-L1 blockade in patients achieving a CR at EOI may prevent PD-L1–driven exhaustion of anti-tumor lymphocytes and maintain activated Teffs, leading to eradication of residual disease and improvement in patients' outcome.

The risk of relapse is higher in patients with advanced DLBCL, which represents the patient population in this study. Relapses occur mostly during the first 2 years following

first-line treatment (Coiffier et al. 2010). Thus, 12 months of consolidation treatment with atezolizumab, for a total treatment duration of approximately 18 months, is considered to be a reasonable exploratory therapeutic approach with an anticipated positive benefit-risk ratio. During consolidation treatment, MRD will be measured to allow for analysis of the benefit of 12 months of consolidation treatment. T-cell receptor repertoire will also be assessed during treatment and after discontinuation of atezolizumab to evaluate the kinetics of atezolizumab-induced immune responses.

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 (^{18}F-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; Cheson et al. 2014).

3.3.4 Rationale for Biomarker Assessments

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

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% versus 56%, respectively; $p < 0.001$)

(Lenz et al. 2008). 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 NHL. 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 NHL, 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 cytotoxic T-lymphocyte-associated protein 4 (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.

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., interleukin [IL]-18, interferon gamma [IFN-γ]) and potential correlation with response to treatment will be assessed in this study.

A recent publication (Rosille et al. 2014) described the prognostic effect of soluble PD-L1 in DLBCL. The prognostic value of soluble PD-L1 levels at baseline will also be assessed in this study. Any effect on PK parameters may also be examined.

3.3.4.3 Rationale for Assessment of Minimal Residual Disease

MRD measurement is an increasingly recognized tool for response assessment in B-cell malignancies. Circulating lymphoma cells and/or tumor DNA can be detected and quantified at low levels as MRD to assess treatment dynamics and monitor patients after treatment. However, there is no scientific proof that MRD is a reliable measure of clinical outcome in NHL, and technical validation of novel technologies for MRD assessment that have clinical utility is still pending.

In FL, MRD at end of treatment is likely to be prognostic (Ladetto et al. 2013). In DLBCL, serum MRD was shown to predict early and late progression after first-line treatment (Roschewski et al. 2014). In addition, MRD assessment may complement the response assessment, particularly in immune treatment–based regimens, and mitigate potential false positive FDG-PET results caused by infiltration of metabolically active ICs into the tumor.

In this study, MRD will be quantified by circulating lymphoma cells and cell-free circulating tumor DNA as an exploratory endpoint.

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
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (see Appendix 9)
- For patients enrolled in the safety run-in phase: lymphoma classified as either of the following:

  Relapsed or refractory FL after treatment with at least one prior chemoimmunotherapy regimen

  Previously untreated Grade 1, 2, or 3a FL that requires treatment, defined as meeting at least one of the Groupe d'Etudes des Lymphomes Folliculaires (GELF) criteria, as listed below:

    Bulky disease, defined as a nodal or extranodal (except spleen) mass ≥7 cm in the greatest diameter

    Local symptoms or compromise of normal organ function due to progressive nodal disease or extranodal tumor mass

    Presence of B symptoms

Presence of symptomatic extranodal disease (e.g., pleural effusions, peritoneal ascites)

Cytopenias due to underlying lymphoma (i.e., ANC $< 1.0 \times 10^9$/L, hemoglobin < 10 g/dL, and/or platelet count $< 100 \times 10^9$/L)

Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm

- For patients enrolled in the expansion phase: lymphoma classified as <u>either</u> of the following:

  Previously untreated Grade 1, 2, or 3a FL that requires treatment, defined as meeting at least one of the GELF criteria (listed above)

  Previously untreated advanced DLBCL, defined as Stage III or IV with an IPI ≥ 2 or Stage II with bulky disease (defined as at least one lesion ≥ 7 cm)

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

  For patients with FL, if the available biopsy was not done within 12 months, a repeat biopsy is strongly recommended.

  Further details are provided in Section 4.5.6.

- For women who are not postmenopausal (≥ 12 consecutive months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 18 months after the last dose of study treatment for patients in the Atezo-G-benda and Atezo-G-CHOP treatment groups or for at least 12 months after the last dose of study treatment for patients in the Atezo-R-CHOP treatment group.

  Examples of non-hormonal contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of progestogen-only hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

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

Barrier methods must always be supplemented with the use of a spermicide.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or 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 3 months after the last dose of study treatment. Men must refrain from donating sperm for the same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study treatment.

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

4.1.2 Exclusion Criteria

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

- Histological evidence of transformation of FL into high-grade B-cell NHL
- Central nervous system lymphoma or leptomeningeal infiltration
- For patients with DLBCL: preplanned consolidative radiotherapy
- 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, 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.

- For patients with relapsed or refractory FL (enrolled in the safety run-in phase)

  Prior allogeneic or autologous SCT

  Prior anthracycline therapy (patients enrolled in the Atezo-G-CHOP treatment group)

  Treatment with fludarabine or alemtuzumab within 12 months prior to Day 1 of Cycle 1

  Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies

  Treatment with a monoclonal antibody, radioimmunoconjugate, or antibody-drug conjugate 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

Clinically significant toxicity (other than alopecia) from prior treatment that has not resolved to Grade ≤2 (per NCI CTCAE v4.0) prior to Day 1 of Cycle 1

- History of solid organ transplantation
- History of severe allergic or anaphylactic reaction to humanized, chimeric, or murine monoclonal antibodies
- Known sensitivity or allergy to murine products
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab, obinutuzumab, rituximab, or bendamustine formulation, including mannitol
- 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.
- 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 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 (see Appendix 13 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.

- 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, Day 1, or anticipation of a major surgical procedure during the course of the study
- For patients who will be receiving CHOP: left ventricular ejection fraction (LVEF) $<50\%$ by multiple-gated acquisition (MUGA) scan or echocardiogram
- Inadequate hematologic function (unless due to underlying lymphoma), defined as follows:

  Hemoglobin <9 g/dL

  ANC $<1.5\times10^9$/L

  Platelet count $<75\times10^9$/L
- 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; see Appendix 14)

  AST or ALT $>2.5\times$ ULN

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

  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 who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to Day 1 of Cycle 1.
- Unable to comply with the study protocol, in the investigator's judgment

4.2 METHOD OF TREATMENT ASSIGNMENT

During the safety run-in phase, patients with FL will be assigned to the Atezo-G-benda or Atezo-G-CHOP induction treatment group at the discretion of the investigator. During the expansion phase, induction treatment will be assigned on the basis of lymphoma histology. Patients with FL will receive Atezo-G-benda induction treatment, and patients

with DLBCL will receive Atezo-R-CHOP induction treatment. Post-induction treatment (for eligible patients only) will also depend on lymphoma histology. Patients with FL will receive Atezo-G maintenance treatment, and patients with DLBCL will receive atezolizumab consolidation treatment (see Section 3.1.2 for details).

Enrollment tracking will be performed through use of an interactive voice or web-based response system (IxRS). Prior to initiating screening, the study site should confirm via the IxRS that slots within the planned treatment group 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 a particular treatment group.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 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 of obinutuzumab. For information on the formulation and handling of obinutuzumab, see the obinutuzumab Investigator's Brochure and Pharmacy Manual.

4.3.1.2 Atezolizumab

Atezolizumab will be supplied by the Sponsor as an IMP. The atezolizumab drug product is provided in a single-use, 20-mL USP/European Pharmacopoeia 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. For information on the formulation and handling of atezolizumab, see the Atezolizumab Investigator's Brochure and Pharmacy Manual.

4.3.1.3 CHOP

CHOP agents will be administered according to the standard preparation and infusion procedures at each investigational site. Refer to the local prescribing information for each agent for information on the formulation, packaging, and handling.

4.3.1.4 Bendamustine

Bendamustine will be supplied by the Sponsor as an IMP. For information on the formulation, packaging, and handling of bendamustine, see the summary of product characteristics for bendamustine.

4.3.1.5 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 4–Table 8 (see Sections 4.3.2.6, 4.3.2.7, and 4.3.2.8).

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

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

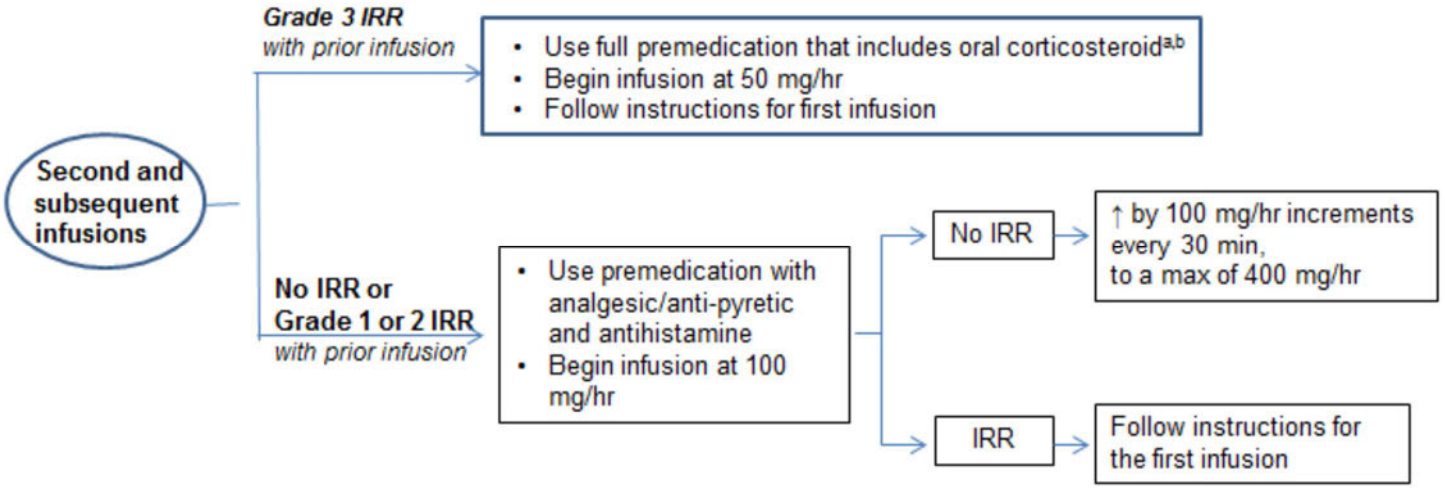
Obinutuzumab will be administered by IV infusion at an absolute (flat) dose of 1000 mg on Days 1, 8, and 15 of the first cycle and on Day 1 of each subsequent cycle during induction treatment, and on Day 1 of every other month (i.e., every 2 months) during maintenance treatment (eligible patients with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

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 extremely 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. Guidelines for treatment delays or discontinuation are provided in Section 5.1.

Premedication with a corticosteroid, analgesic/antipyretic, and antihistamine, as outlined in Section 4.3.2.9 (see Table 9), is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 12.

Figure 2 Guidelines for Obinutuzumab Infusions: First Infusion

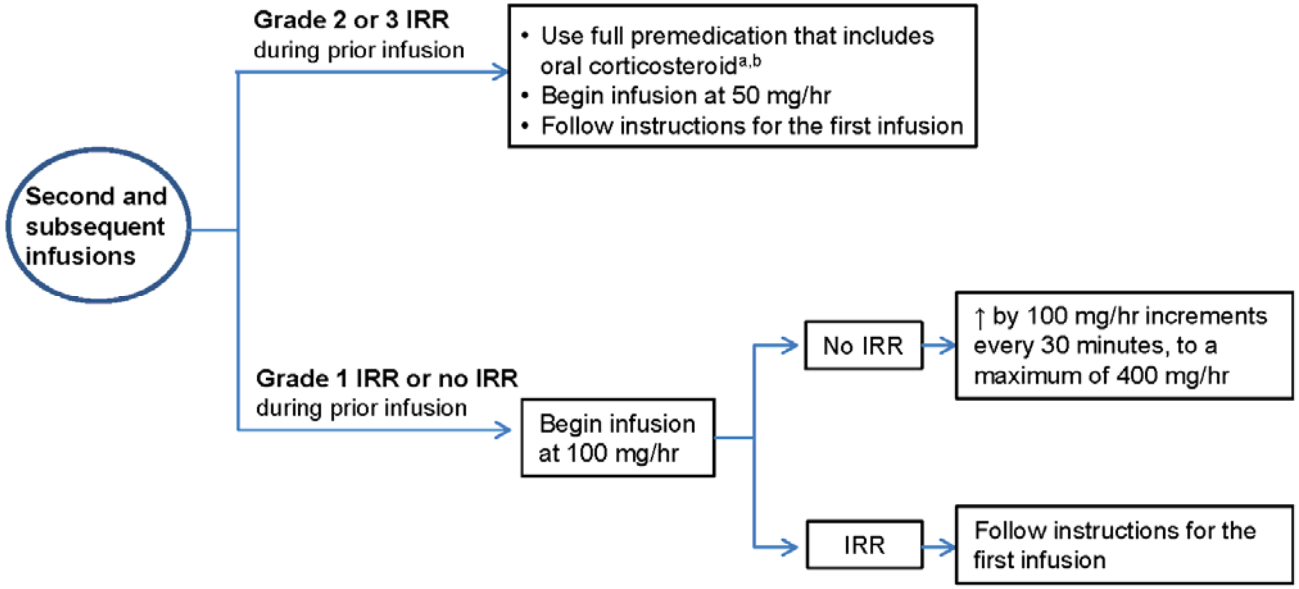


IRR = infusion-related reaction.

[a] All patients should receive full premedication with an oral corticosteroid, oral analgesic/anti-pyretic, antihistamine, and anti-emetic prior to the first obinutuzumab infusion. Refer to Section 4.3.2.9 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 12.

Figure 3 Guidelines for Obinutuzumab Infusions: Second and Subsequent Infusions



IRR = infusion-related reaction.

[a] Patients should receive full premedication with an oral corticosteroid, oral analgesic/anti-pyretic, and antihistamine prior to the obinutuzumab infusion. Refer to Section 4.3.2.9 for details.

[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 will be administered at a flat dose consisting of one of the following: a) 1200 mg q3w (1200 mg on Day 1 of Cycles 2 and beyond, given in 21-day cycles either with G-CHOP as induction treatment or alone as consolidation treatment); b) 840 mg q2w (840 mg on Days 1 and 15 of Cycles 2–6, given in 28-day cycles with G-benda as induction treatment); or c) 1680 mg q4w (840 mg on Days 1 and 2 of each month, given with obinutuzumab as maintenance treatment). Detailed atezolizumab dosing regimens are provided in Table 4 and Table 5 for induction treatment and in Table 7 and Table 8 for post-induction treatment (see Sections 4.3.2.6, 4.3.2.7, and 4.3.2.8).

Atezolizumab infusions will be administered as follows:

- The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes.
- In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a moderate (NCI CTCAE Grade 2) IRR or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved. The infusion rate at restart should be half of the infusion rate being given at the time of event onset.
- In the event of a severe or life-threatening (NCI CTCAE Grade 3 or 4) IRR, the infusion should be stopped immediately, aggressive resuscitation and supportive measures should be initiated, and atezolizumab should be permanently discontinued.

For anaphylaxis precautions, see Appendix 12.

No dose modification for atezolizumab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.

4.3.2.3 CHOP

Each CHOP agent will be administered at the standard dose and schedule, according to the standard preparation and infusion procedures of each investigational site (see Section 4.3.2.7 for details).

4.3.2.4 Bendamustine

For the Atezo-G-benda treatment group, bendamustine will be administered by IV infusion at a dose of 90 mg/m^2 on Days 1 and 2 of each 28-day cycle, for up to 6 cycles. There must be a minimum of 12 hours between each bendamustine administration.

Body surface area (BSA) will be determined at screening and should be used to calculate the dose of bendamustine throughout the study unless the patient's weight increases or decreases by >10% from screening, in which case BSA should be recalculated and used for subsequent dosing. In obese patients (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.

4.3.2.5 Rituximab

Rituximab will be administered by IV infusion at the dose of 375 mg/m^2 on Day 1 of Cycles 1−8. BSA will be determined at screening and used as described in Section 4.3.2.4.

The infusion of rituximab may be split over 2 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 2 days, both infusions must occur with appropriate premedication (see Section 4.3.2.9) and at the first infusion rate (see Table 3).

Rituximab infusions will be administered according to the instructions in Table 3. 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 3 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 5.1.7.

Premedication with a corticosteroid, analgesic/antipyretic, and antihistamine, as outlined in Section 4.3.2.9, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 12.

4.3.2.6 Induction Treatment with Atezo-G-Benda

Patients in the Atezo-G-benda treatment group will receive induction treatment, administered in 28-day cycles, as follows:

- Patients will receive 6 cycles of induction treatment consisting of obinutuzumab and bendamustine for Cycles 1–6 and for Cycles 2–6, as outlined in Table 5.

Premedication should be administered as described in Section 4.3.2.9.

Obinutuzumab will be administered first, followed by a line flush (unless there is a central line with more than one line/port), after which atezolizumab will be administered. Bendamustine will be administered at least 30 minutes after atezolizumab infusion. If it is the strong preference of the investigator or the site (e.g., for logistical reasons), the administration of bendamustine prior to obinutuzumab is allowed. In this case, obinutuzumab should be administered within 30 minutes after bendamustine infusion.

For patients at increased risk for IRRs (high tumor burden), the obinutuzumab infusion may be split and administered over 2 days.

For patients who experience an adverse event during obinutuzumab infusion, administration of atezolizumab and bendamustine may be delayed by 1 day if clinically required. If bendamustine is delayed, subsequent bendamustine infusions should be delayed by the same number of days to maintain the regular bendamustine cycle interval of 28 days.

Table 4 Induction Treatment: Atezo-G-Benda Treatment Group

Treatment	Dose	Route	Regimen (28-day cycles)	
			Cycle 1	Cycles 2–6
Obinutuzumab	1000 mg	IV	Days 1, 8, and 15	Day 1
Bendamustine	90 mg/m^2	IV	Days 1 and 2	Days 1 and 2
Atezolizumab	840 mg	IV	—	Days 1 and 15

Atezo = atezolizumab; Benda = bendamustine; G = obinutuzumab; IV = intravenous.

4.3.2.7 Induction Treatment with Atezo-G-CHOP or Atezo-R-CHOP

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

- Patients enrolled in the safety run-in phase (i.e., patients with FL) will receive 6 cycles of induction treatment consisting of obinutuzumab and CHOP for Cycles 1–6 and atezolizumab for Cycles 2–6, as outlined in Table 5.
- Patients enrolled in the expansion phase (i.e., patients with DLBCL) will receive 8 cycles of induction treatment consisting of rituximab for Cycles 1–8, atezolizumab for Cycles 2–8, and CHOP for either Cycles 1–6 or Cycles 1–8 as determined by the investigator, as outlined in Table 5.

Premedication should be administered as described in Section 4.3.2.9.

Oral prednisone (or prednisolone, if prednisone is unavailable) should be administered first, at least 60 minutes prior to commencing study treatment infusions. Obinutuzumab or rituximab will be administered second, followed by a line flush (unless there is a central line with more than one line/port). Then atezolizumab will be administered followed by a line flush. Finally, chemotherapy components will be administered. The order of administration of cyclophosphamide, doxorubicin, and vincristine will be determined by local institutional practice.

The 40 mg/m^2 dose of prednisone on Day 1 will be replaced by oral corticosteroids given as premedication on Day 1 of Cycle 1 (and subsequent cycles as indicated). Details on corticosteroid premedication are provided in Section 4.3.2.9.

For patients at increased risk for IRRs (high tumor burden), the obinutuzumab and rituximab infusions may be split and administered over 2 days.

For patients who experience an adverse event during obinutuzumab or rituximab infusion, administration of atezolizumab and CHOP may be delayed by 1 day if clinically required. If CHOP is delayed, subsequent CHOP administration should be delayed by the same number of days to maintain the regular CHOP cycle interval of 21 days.

Table 5 Induction Treatment, Safety Run-In Phase: Atezo-G-CHOP Treatment Group

Treatment	Dose	Route	Regimen (21-day cycles)	
			Cycle 1	Cycles 2–6
Obinutuzumab	1000 mg	IV	Days 1, 8, and 15	Day 1
Cyclophosphamide	750 mg/m^2	IV	Day 1	Day 1
Doxorubicin	50 mg/m^2	IV	Day 1	Day 1
Vincristine	1.4 mg/m^2 (maximum, 2 mg)	IV	Day 1	Day 1
Prednisone [a]	40 mg/m^2	Oral	Days 1–5	Days 1–5
Atezolizumab	1200 mg	IV	—	Day 1

Atezo = atezolizumab; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; G = obinutuzumab; IV = intravenous.

[a] Prednisolone may be given if prednisone is unavailable. The 40 mg/m^2 dose of prednisone on Day 1 will be replaced by oral corticosteroids given as premedication on Day 1 of Cycle 1 (and subsequent cycles as indicated) (see details on premedication in Section 4.3.2.9).

Table 6 Induction Treatment, Expansion Phase: Atezo-R-CHOP

Treatment	Dose	Route	Regimen (21-day cycles)	
			Cycle 1	Cycles 2–6/8 [a]
Rituximab	375 mg/m^2	IV	Day 1	Day 1
Cyclophosphamide	750 mg/m^2	IV	Day 1	Day 1
Doxorubicin	50 mg/m^2	IV	Day 1	Day 1
Vincristine	1.4 mg/m^2 (maximum, 2 mg)	IV	Day 1	Day 1
Prednisone [b]	40 mg/m^2	Oral	Days 1–5	Days 1–5
Atezolizumab	1200 mg	IV	—	Day 1

Atezo = atezolizumab; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; IV = intravenous; R = rituximab.

[a] Patients will receive eight cycles of induction treatment consisting of rituximab for Cycles 1–8, atezolizumab for Cycles 2–8, and CHOP for either Cycles 1–6 or Cycles 1–8, as determined by the investigator.

[b] Prednisolone may be given if prednisone is unavailable. The 40 mg/m^2 dose of prednisone on Day 1 will be replaced by oral corticosteroids given as premedication on Day 1 of Cycle 1 (and subsequent cycles as indicated) (see details on premedication in Section 4.3.2.9).

4.3.2.8 Post-Induction Treatment

Patients with DLBCL (i.e., patients treated with Atezo-R-CHOP during the expansion phase) who achieve a CR at EOI will receive post-induction treatment (referred to as consolidation) with atezolizumab, administered in 21-day cycles for 17 cycles, as outlined in Table 7. Patients with FL who achieve a CR or PR at EOI will receive post-induction treatment (referred to as maintenance) with atezolizumab and obinutuzumab for approximately 24 months, as outlined in Table 8. Obinutuzumab will be administered first, followed by a line flush (unless there is a central line with more than one line/port), after which atezolizumab will be administered. Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity for up to 1 year for consolidation treatment or 2 years for maintenance treatment.

Table 7 Consolidation Treatment for Patients with DLBCL

Treatment	Dose	Route	Regimen (21-day cycles)
Atezolizumab	1200 mg	IV	Day 1 of Cycles 9–25

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

Table 8 Maintenance Treatment for Patients with FL

Treatment	Dose	Route	Regimen (total of 24 months[a])
Obinutuzumab	1000 mg	IV	Day 1 of every other month (starting with Month 1)
Atezolizumab	840 mg	IV	Days 1 and 2 of each month

FL = follicular lymphoma; IV = intravenous.

[a] 1 month = 28 days.

4.3.2.9 Premedication

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]	Complete ≥ 1 hour prior to obinutuzumab or rituximab infusion.
	• All patients	• Oral analgesic/anti-pyretic [b] • Antihistamine drug [c]	Administer ≥ 30 minutes prior to obinutuzumab or rituximab infusion.
	• All patients	• Serotonin (5-HT3) antagonist (e.g., dolasetron, ondansetron) or another anti-emetic	Administer 30 minutes prior to initiation of study treatment, on Day 1 for patients receiving CHOP and on Days 1 and 2 for patients receiving bendamustine.
	• 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. For patients in Atezo-G-benda treatment group, allopurinol should be started 72 hours prior to bendamustine infusion and stopped 24 hours prior to bendamustine infusion.
Cycle 1, Days 8 and 15 Cycles 2 and Beyond, Day 1	• Patients with no IRR or 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. For patients receiving rituximab who do not experience any IRR with their previous infusion, premedication may be omitted at the investigator's discretion.
	• Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion • Patients with bulky disease	• Oral corticosteroid a	Complete ≥ 1 hour prior to obinutuzumab or rituximab infusion.
		• Antihistamine drug [b] • Oral analgesic/anti-pyretic [c]	Administer at least 30 minutes prior to obinutuzumab or rituximab 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. For patients in Atezo-G-benda treatment group, allopurinol should be started 72 hours prior to bendamustine infusion and stopped 24 hours prior to bendamustine infusion.

Table 9 Premedication (cont.)

Timepoint	Patients Requiring Premedication	Premedication	Administration
Cycles 2–6/8	• All patients receiving chemotherapy	• Serotonin (5-HT3) antagonist (e.g., dolasetron, ondansetron) or another anti-emetic	Administer 30 minutes prior to initiation of study treatment, on Day 1 for patients receiving CHOP and on Days 1 and 2 for patients receiving bendamustine.

Atezo-G-benda = atezolizumab in combination with obinutuzumab plus bendamustine; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; 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, as it has not been effective in reducing rates of IRR. On Day 1, the premedication oral corticosteroid dose (100 mg of prednisone or prednisolone, or 80 mg of methylprednisolone) will be given in place of the 40-mg/m^2 prednisone dose for patients treated with Atezo-G-CHOP or Atezo-R-CHOP.

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

[c] For example, 50 mg of diphenhydramine.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (obinutuzumab, rituximab, atezolizumab, and bendamustine) 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.

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

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

4.3.4 Post-Trial Access to Obinutuzumab, Rituximab, Atezolizumab, and Bendamustine

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 screening to the treatment completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Premedication should be administered as described in Section 4.3.2.9.

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

Primary prophylaxis with G-CSF is recommended according to American Society of Clinical Oncology, EORTC, and European Society for Medical Oncology guidelines (Smith et al. 2015), or per each site's institutional standards. Additionally, G-CSF prophylaxis is strongly recommended in Cycle 1 for all patients in the Atezo-G-CHOP and Atezo-G-benda treatment groups, given the expected myelosuppressive effect of these combinations.

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 low-molecular-weight heparin (LMWH) prior to Day 1 of Cycle 1.

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

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:

- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor (denosumab) for a period of 10 weeks after the last dose of atezolizumab

  RANKL inhibition could potentially alter the activity and safety of atezolizumab. Thus, patients receiving a RANKL inhibitor prior to enrollment must be willing and eligible to receive a bisphosphonate instead of a RANKL inhibitor.
- Any anti-cancer therapy, approved or investigational, other than intrathecal central nervous system prophylaxis
- Hormonal therapy other than contraceptives, stable hormone-replacement therapy, or megestrol acetate
- Biologic agents other than hematopoietic growth factors (as described in Section 4.4.1)
- Immunostimulatory agents, including, but not limited to, interferon alpha (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 5 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, Appendix 2, and Appendix 3 for the schedules of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-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, Appendix 2, and Appendix 3); 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.

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 7 days prior to the screening visit 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 9)
- B symptoms (unexplained fever $>38°C$, night sweats, unexplained weight loss $>10\%$ of body weight over 6 months)
- Ann Arbor staging (see Appendix 10)
- For patients with FL: Follicular Lymphoma International Prognostic Index (FLIP)I and FLIPI2 (see Appendix 11)
- For patients with DLBCL: IPI (see Appendix 11)
- For patients with relapsed or refractory FL: 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, Appendix 2, and Appendix 3), 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 described 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 IRC and the investigator on the basis of physical examinations (see Section 4.5.3), PET and CT scans, and bone marrow examinations using the Lugano 2014 criteria (see Appendix 7). and the modified Cheson 2007 criteria (see Appendix 8). 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.

4.5.5.1 Radiographic Assessments

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

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

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 this allows 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.

4.5.5.2 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 and continued bone marrow involvement, 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.

4.5.6 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, other cells)
- Serum chemistry: sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase (ALP), amylase, lipase, LDH, uric acid
- Thyroid-stimulating hormone (TSH), triiodothyronine, thyroxine (T4)
- β_2 microglobulin
- Coagulation: INR, aPTT (or PTT), PT
- Pregnancy test

  All women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening (within 7 days of Day 1 of Cycle 1) and at the end of treatment.
- Viral serology

  Hepatitis B testing includes HBsAg and total HBcAb.

  Hepatitis C testing includes HCV antibody.
- Quantitative immunogloblulins: IgA, IgG, 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 atezolizumab (MPDL3280A) PK analysis using a validated assay
- Serum samples for rituximab PK analysis using a validated assay
- Serum samples for assessment of HACAs to rituximab using a validated assay
- Serum samples for assessment of HAHAs to obinutuzumab using a validated assay
- Serum samples for assessment of ATAs to atezolizumab (MPDL3280A) using validated assays
- 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 fewer 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 above criteria, a pretreatment core-needle, excisional, or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.

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 (see 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

Sample Type	Timing	Proposed Non-Inherited Biomarkers
Archival or fresh tumor tissue	Prior to study (archival) or baseline (fresh)	• For DLBCL patients only: DLBCL cell-of-origin subtype (ABC vs. GCB), BCL2, MYC, Epstein-Barr virus status • 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
Plasma	Baseline	• Soluble PD-L1
Plasma	Baseline and subsequent timepoints during treatment	• Cytokines characteristic of T-cell activation (e.g., IL-18, IFN-γ)
Whole blood (separated into PBMCs and plasma)	Baseline and subsequent timepoints during treatment	Detection of minimal residual disease: • Cell-free circulating tumor DNA in plasma • Circulating lymphoma cells in PBMCs
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; BCL2 = B-cell lymphoma 2 gene; DBLCL = diffuse large B-cell lymphoma; GCB = germinal-center B-cell–like; HLA-1 = human lymphocyte antigen; IFN-γ = interferon gamma; IL = interleukin; NK = natural killer; PBMCs = peripheral blood mononuclear cells; PD-L1 = programmed death-ligand 1.

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).

4.5.7 Electrocardiograms

Single, resting, 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedules of assessments (see Appendix 1, Appendix 2, and Appendix 3), 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.

4.5.8 Echocardiogram or MUGA

For patients receiving CHOP, LVEF will be assessed by echocardiography or MUGA scan at specified timepoints, as outlined in the schedules of assessments (see Appendix 1, Appendix 2, and Appendix 3).

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. 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 is 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, or NHL:

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

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

4.5.9.4 Confidentiality

Confidentiality for All RCR 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 the Sponsor's 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 Sponsor 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 the Sponsor, except where agreed otherwise.

Additional Confidentiality for Specimens Used for Genetic Research

Given the sensitive nature of genetic data, the Sponsor 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 the Sponsor'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 BO29563 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 BO29563.

4.5.9.7 Monitoring and Oversight

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

- Hematologic toxicity that is related to study treatment and consists of either of the following:

  Grade ≥ 3 hematologic adverse event that requires study treatment to be withheld > 21 days in patients with FL and > 14 days in patients with DLBCL

  Recurrent Grade 4 neutropenia with infection, despite G-CSF support and dose modifications

- Non-hematologic toxicity that consists of either of the following:

  Grade ≥3 non-hematologic adverse event that has a reasonable possibility of being related to study treatment and either is life threatening or requires study treatment to be withheld for >21 days in patients with FL and >14 days in patients with DLBCL

  Development of an atezolizumab-related immune-related adverse event that is life threatening or requires atezolizumab to be withheld for >42 days, unless approved by the Medical Monitor

- Disease progression

  Cases of apparent radiographic progression (pseudoprogression/tumor immune infiltration), including the appearance of new lesions have been described in patients with solid tumors treated with immunotherapies (Wolchok et al. 2009). 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

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 safety run-in phase, patients who discontinue study treatment prior to completing Cycle 3 for reasons other than toxicity will be replaced.
- During the expansion phase, patients who discontinue from the study after Cycle 1 (i.e., prior to receiving atezolizumab) 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, atezolizumab, and bendamustine) are outlined below.

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 5.1.7).

5.1.1 Risks Associated with Obinutuzumab

The following adverse events are considered to be important risks associated or potentially associated with obinutuzumab: IRRs and hypersensitivity reactions, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia), 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 and Hypersensitivity 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 hypotension, fever, chills, dyspnea, flushing, nausea, vomiting, hypertension, fatigue, 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 5.1.7.3 and Appendix 12.

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. In the case a hypersensitivity reaction is suspected during or after an infusion, the infusion should be stopped and treatment permanently discontinued.

5.1.1.2 Tumor Lysis Syndrome

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 4.3.2.9 (see Table 9). Additional guidelines for management of TLS in this study are provided in Section 5.1.7.2 (see Table 14).

5.1.1.3 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 $\geq$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. The use of G-CSF is allowed for treatment of neutropenia in this study. Prophylactic treatment with antibiotics should be administered as per standard practice. Guidelines for primary prophylaxis with G-CSF are provided in Section 4.4.1.

5.1.1.4 Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. In CLL patients 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.

5.1.1.5 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 FL studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen during maintenance. Details are provided in the Obinutuzumab Investigator's Brochure.

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 positive for HBsAg and HBcAb are not eligible for this study.

John Cunningham (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 Table 13.

5.1.1.6 Immunizations

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

5.1.1.7 Worsening of Preexisting Cardiac Condition

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

5.1.1.8 Gastrointestinal Perforation

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: IRRs, infections (including PML and HBV reactivation), neutropenia (including prolonged), rTLS, impaired immunization response, GI perforation, and severe mucotanous reactions. Details for some of 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 $\geq$1/1,000 and $<$1/100 patients) and are rarely fatal (occurring in $\geq$1/10,000 and $<$1/1,000 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. These are related to cytokine release, and these acute IRRs overlap with "cytokine release syndrome". Anaphylactic and other hypersensitivity reactions also occur 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. New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C viruses.

5.1.2.3 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 $<$1/10,000 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, 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.

5.1.2.4 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 $<$1/10,000 patients), based on postmarketing experience. Signs and symptoms (e.g. hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated LDH) that are consistent with TLS have been reported to occur after the first MabThera/Rituxan IV infusion in patients with high numbers of circulating malignant lymphocytes. A high number of circulating malignant cells ($\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.

5.1.2.5 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.

5.1.2.6 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.

5.1.2.7 Severe Mucocutaneous Reactions

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic

epidermal necrolysis (TEN). The onset of these reactions in patients treated with rituximab has varied from 1–13 weeks following rituximab exposure.

5.1.2.8 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, 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 Bendamustine

5.1.4.1 Myelosuppression

Bendamustine caused severe myelosuppression (Grade ≥3) in 98% of patients in the two bendamustine single-agent studies (Friedberg et al. 2008; Kahl et al. 2010). Hematologic nadirs were observed predominantly in the third week of therapy. Patients who experience Grade 3 or 4 neutropenia or thrombocytopenia should be monitored until neutrophil and platelet values return to at least Grade 2. The use of G-CSF for primary prophylaxis and treatment of neutropenia is permitted in this study. Myelosuppression may require dose delays and/or subsequent dose reductions if recovery to the recommended values has not occurred by the first day of the next scheduled cycle. Guidelines for management of hematologic toxicities are provided in Section 5.1.7.2.

5.1.4.2 Infection

Infection, including pneumonia and sepsis, has been reported with bendamustine administration. Patients with myelosuppression after treatment with bendamustine are more susceptible to infections. The study physician will treat patients with clinical evidence of infection appropriately.

5.1.4.3 Infusion-Related Reactions and Anaphylaxis

Infusion reactions to bendamustine have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus, and rash. In rare instances, severe anaphylaxis and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy.

5.1.4.4 Tumor Lysis Syndrome

TLS has been reported in association with bendamustine treatment in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of bendamustine and, without intervention, may lead to acute renal failure and death. 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 4.3.2.9 (see Table 9). Additional guidelines for management of TLS in this study are provided in Section 5.1.7.3 (see Table 15).

5.1.4.5 Skin Reactions

Skin reactions have been reported with bendamustine treatment, including rash, toxic skin reactions, and bullous exanthema. In a study of bendamustine in combination with rituximab, one case of TEN occurred. Cases of Stevens−Johnson syndrome and TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to bendamustine cannot be determined. Patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, bendamustine should be withheld.

5.1.4.6 Long-Term Stem-Cell Toxicity

There are reports of premalignant and malignant diseases that have developed in patients treated with bendamustine, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma. The association with bendamustine therapy has not been determined.

5.1.4.7 Extravasation Injury

Bendamustine extravasations have been reported, resulting in hospitalizations from erythema, marked swelling, and pain. Precautions should be taken to avoid extravasation, including monitoring of the IV infusion site for redness, swelling, pain, infections, and necrosis during and after administration of bendamustine.

5.1.4.8 Drug Interactions

Certain medications may interact with bendamustine. Caution should be used or alternative treatments should be considered if concomitant treatment with cytochrome P450 (CYP)1A2 inhibitors or inducers is needed. CYP1A2 inhibitors and inducers are not contraindicated.

During treatment with bendamustine, patients will be provided with a card to keep with them that provides notification to other health care providers that the patient is taking bendamustine as a participant in a clinical study (see Appendix 13).

5.1.5 Risks Associated with CHOP

Refer to prescribing information for doxorubicin, cyclophosphamide, vincristine, and prednisone for risks related to CHOP chemotherapy.

5.1.6 Risk of Overlapping Toxicities

The anticipated toxicities from the combined administration of atezolizumab and obinutuzumab, with either CHOP or bendamustine, and of atezolizumab with rituximab and CHOP are expected to be manageable in this clinical trial. A summary of anticipated overlapping toxicities is presented in Table 11.

Obinutuzumab was safely combined with CHOP in patients with previously untreated DLBCL (n = 100) or relapsed or refractory FL (n = 38), and with bendamustine in patients with previously untreated FL (n = 37). Neutropenia and infections (mainly neutropenic infections) appeared to be the most important adverse events associated with these combinations but were manageable with prophylactic administration of G-CSF and appropriate management of infections (Dyer et al. 2012; Zelenetz et al. 2013). Rituximab in combination with CHOP is the standard of care in previously untreated DLBCL and is generally well tolerated, with the main toxicities being myelosuppression and infections.

There is no anticipated risk of overlapping hematologic toxicity when combining atezolizumab with G-CHOP, R-CHOP, or G-benda. Thus, the Atezo-G-CHOP, Atezo-R-CHOP, and Atezo-G-benda regimens will likely be associated with a manageable risk of myelosuppression and infections in the clinical setting. In addition to the standard hematologic monitoring, patients enrolled in this study will be closely monitored for evidence of infections.

Atezolizumab has a minimal risk of overlapping non-hematologic toxicity with G-CHOP, R-CHOP, and G-benda, limited to potentially increased risk of IRRs, GI toxicity (nausea, vomiting, and diarrhea), dermatologic reactions, and impaired liver function. These risks will be addressed by standard monitoring for IRRs, premedication for nausea/vomiting, and close clinical monitoring for any evidence of skin reactions, diarrhea, or hepatic abnormalities. The potential risk of increased liver toxicity is substantially mitigated by excluding patients who are positive for HBV and HCV from enrollment in the study.

Table 11 Summary of Potentially Overlapping Adverse Events

Event		Atezolizumab [a]	Obinutuzumab [b,c]	Rituximab [b]	G-CHOP [d]	R-CHOP [d]	G-Benda [e]
Hematologic Toxicity							
Neutropenia, Grade 3 or 4		0	5%–14%	7%	46.2%	38.1%	29%
Febrile neutropenia		0	2%–5%	1%	17.5%	15.2%	5.3%
Thrombocytopenia, Grade 3 or 4		0	5%–8%	0	4.4%	1.4%	10%
Anemia, Grade 3 or 4		4.6%	3%	1%	7.2%	7.5%	7%
Non-Hematologic Toxicity							
IRRs	All grades	1.2%	73%–75%	51%	36%	23.5%	59%
	Grade 3 or 4	0	11%	5%	2.8%	0.6%	10%
Infections	All grades	0	5%–41%	49%	53.8%	44%	15%
	Grade 3 or 4	0	3%–10%	6%	19.2% [f]	15.5% [f]	10%
Rash	All grades	13%	7%	3%	2.3%	6.4%	12%
	Grade 3 or 4	0	0	0	0.1%	0.1%	
Diarrhea	All grades	22.4% [g]	5%–8%	8%	16%	13%	34%
	Grade 3 or 4	0	0	0	2.1%	1.3%	2%
Vomiting	All grades	19.7%	5%	3%	14.6%	10.5%	15%
	Grade 3 or 4	0.2%	0	0	1%	0.3%	0

Table 11 Summary of Potentially Overlapping Adverse Events (cont.)

Event		Atezolizumab [a]	Obinutuzumab [b,c]	Rituximab [b]	G-CHOP [d]	R-CHOP [d]	G-Benda [e]
Nausea	All grades	27.8%	5%–9%	8%	29.4%	28.3%	56%
	Grade 3 or 4	0.2%	0	0	1.8%	0.3%	5%
SGOT/SGPT increase	Grade 3 or 4	1.7% [g]	3%	1%	< 1%	< 1%	0

G-Benda = obinutuzumab plus bendamustine; G-CHOP = obinutuzumab plus CHOP chemotherapy; R-CHOP = rituximab plus CHOP chemotherapy.

[a] Atezolizumab Investigator's Brochure, Version 9, August 2016.

[b] BO21003 CSR (No. 1056428).

[c] BO20999 CSR (No. 1036614) (high dose, NHL cohorts).

[d] Study BO21005/Outputs dated 14 July 2016.

[e] BO21000 CSR (No. 1051870) (adverse events during induction).

[f] The most frequent Grade 3–4 infection was pneumonia (4%).

[g] Grade 2 immune colitis and Grade 3 or 4 immune hepatitis were documented in 0.4% and 0.7% of patients, respectively.

5.1.7 Management of Specific Adverse Events

Patients should be assessed clinically before each study treatment administration. Guidelines for management of toxicities are based on laboratory values obtained within 72 hours prior to Day 1 of each cycle or within 24 hours prior to Days 8 and 15 of Cycle 1. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable.

There will be no dose reductions of obinutuzumab, rituximab, or atezolizumab. 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 toxicities that are considered to be related to any of the study treatment components. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications.

Guidelines for management of toxicities during induction treatment are provided in Section 5.1.7.2. Guidelines for management of toxicities during consolidation or maintenance treatment 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.

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 toxicities identified or ongoing at administration of obinutuzumab on Day 8 or 15 or atezolizumab on Day 15. Table 13 provides

guidelines for management of hematologic toxicities that are identified or ongoing at administration of obinutuzumab on Day 8 or 15 or atezolizumab on Day 15 when patients are to receive treatment with obinutuzumab or atezolizumab only. Hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia. Lymphopenia is not considered hematologic toxicity, but an expected outcome of therapy.

Table 12 Guidelines for Management of Hematologic Toxicities during Induction Treatment (Except at Administration of Obinutuzumab on Day 8 or 15 or Atezolizumab on Day 15)

Event	Action to Be Taken
Grade 3 or 4 hematologic toxicity [a,b,c]	**For patients who have had one or no prior chemotherapy dose reductions:** • 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 who develop platelet count of <20,000/μL while receiving LMWH, reduce the dose of LMWH. For patients who develop platelet count of <20,000/μL while receiving platelet inhibitors, consider temporarily withholding platelet inhibitors. • If improvement to Grade ≤2 or baseline within 7 days after the scheduled date for the next cycle in patients with DLBCL or within 13 days after the scheduled date for the next cycle in patients with FL, resume obinutuzumab/rituximab and atezolizumab at full dose and resume chemotherapy components at current dose. • If improvement to Grade ≤2 or baseline 8–14 days after the scheduled date for the next cycle in patients with DLBCL or 14–21 days after the scheduled date for the next cycle in patients with FL, resume obinutuzumab/rituximab and atezolizumab at full dose and resume chemotherapy components at a reduced dose [a,b] for current and subsequent cycles as outlined below: First reduction – Atezo-G-CHOP or Atezo-R-CHOP: Decrease cyclophosphamide dose to 500 mg/m^2 and doxorubicin dose to 35 mg/m^2. – Atezo-G-benda: Decrease bendamustine dose to 70 mg/m^2. Second reduction – Atezo-G-CHOP or Atezo-R-CHOP: Decrease cyclophosphamide dose to 375 mg/m^2 and doxorubicin dose to 25 mg/m^2. – Atezo-G-benda: Decrease bendamustine dose to 50 mg/m^2. No more than two dose reductions of chemotherapy are allowed. • If study treatment is withheld for >14 days in patients with DLBCL or for >21 days in patients with FL, permanently discontinue study treatment. **For patients who have had two prior chemotherapy dose reductions:** • Permanently discontinue study treatment.

Atezo = atezolizumab; benda = bendamustine; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; DBLCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; G = obinutuzumab; G-CSF = granulocyte colony-stimulating factor; LMWH = low-molecular-weight heparin NHL = non-Hodgkin's lymphoma; R = rituximab.

[a] Treatment delays apply to all toxicities; dose modifications apply only to toxicities that are considered to be related to any of the study treatment components. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications.

[b] If cytopenia is thought to be caused mainly by NHL infiltration of the bone marrow, the investigator may decide not to reduce the chemotherapy doses.

Table 13 Guidelines for Management of Hematologic Toxicities during Induction Treatment at Administration of Obinutuzumab on Day 8 or 15 or Atezolizumab on Day 15

Event	Action to Be Taken
Febrile neutropenia or neutropenia with infection	• Withhold obinutuzumab and atezolizumab until resolution of fever and infection (as applicable). • If the event is ongoing on Day 1 of the subsequent cycle, follow instructions in Table 12. Note: Obinutuzumab and atezolizumab should not be withheld for asymptomatic neutropenia.
Severe thrombocytopenia [a] or bleeding	• Withhold obinutuzumab and atezolizumab until platelet count $\geq$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 on Day 1 of the subsequent cycle, 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.

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. • If study treatment is withheld for >21 days in patients with FL and > 14 days in patients with DLBCL because of a toxicity that is attributable to obinutuzumab/rituximab and/or chemotherapy, permanently discontinue all study treatment. • When a treatment cycle is delayed because of toxicity resulting from any component of the regimen, all study treatment should generally be held and resumed together to remain synchronized. However, if it is anticipated that atezolizumab will be delayed by > 21 days in patients with FL and > 14 days in patients with DLBCL, obinutuzumab/rituximab and chemotherapy should be given without atezolizumab if there is no contraindication. • 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, please refer to the Atezolizumab Investigator's Brochure. • If a life-threatening immune-related toxicity occurs, or if atezolizumab is withheld for >42 days because of an immune-related toxicity, permanently discontinue atezolizumab, unless approval for continued treatment is granted by the Medical Monitor. • If atezolizumab is permanently discontinued because of toxicity solely attributable to atezolizumab, obinutuzumab/rituximab and chemotherapy may be continued at the investigator's discretion if agreed to by the Medical Monitor.
IRRs and anaphylaxis	• Guidelines for the management of IRRs are provided in Section 4.3.2.1 for obinutuzumab and rituximab and Section 4.3.2.2 for atezolizumab. Anaphylaxis precautions are provided in Appendix 12. • 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 and Atezolizumab Investigator's Brochure
TLS	• Withhold study treatment. • Perform chemistry panel on a regular bases during the first week [a] • 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 have resolved completely, resume obinutuzumab/rituximab and atezolizumab at full dose and resume chemotherapy components at current dose.

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

Event		Action to Be Taken
Hemorrhagic cystitis		• Withhold Atezo-G-CHOP or Atezo-R-CHOP [a] • If improvement to Grade ≤1, resume Atezo-G-CHOP or Atezo-R-CHOP with the cyclophosphamide dose decreased to 500 mg/m^2 (no modifications for other treatment components). [a] Mesna and hydration during the next administration of cyclophosphamide is recommended. • If symptoms do not recur, cyclophosphamide dose may be increased to 750 mg/m^2 for subsequent cycles.
Peripheral neuropathy	Grade 4 or Myasthenia gravis (any grade) or Guillain-Barre (any grade)	• Permanently discontinue study treatment.
	Grade 2 or 3	• Withhold Atezo-G-CHOP or Atezo-R-CHOP. [a] • If improvement to Grade ≤ 1 or baseline, resume Atezo-G-CHOP or Atezo-R-CHOP with the vincristine dose decreased to 0.7 mg/m2 (maximum, 1 mg) for current and subsequent cycles (no modifications for other treatment components). [a] • Permanently discontinue atezolizumab for life-threatening immune-related neuropathy.
New-onset neurologic manifestations suggestive of PML		• Withhold study treatment. [a] • Consult with a neurologist if PML is suspected (refer to Section 5.1.1.5 for guidance on investigations). • If PML is ruled out, resume obinutuzumab and atezolizumab or atezolizumab and rituximab at full dose and resume chemotherapy components at current dose. • If PML is confirmed, permanently discontinue study treatment.
Immune-related meningoencephalitis		• Withhold study treatment. • Refer patient to neurologist. • 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: –Resume obinutuzumab/rituximab at full dose and chemotherapy components at current dose. – Taper corticosteroids over ≥ 1 month. Contact the Medical Monitor before resuming atezolizumab.

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

Event		Action to Be Taken
AST, ALT, or bilirubin increase	Grade ≥3 (or ≥10 × ULN for patients with liver involvement)	• Withhold study treatment [a] and monitor liver enzymes at least every 7 days. • Investigate etiology. Consult with a hepatologist if immune etiology is suspected (refer to the Atezolizumab Investigator's Brochure for guidance in case of suspected immune-related hepatitis). • For immune-related hepatopathy: –Treat with corticosteroids following guidance provided in the Atezolizumab Investigator's Brochure –Permanently discontinue atezolizumab –Obinutuzumab/rituximab may be resumed at full dose and chemotherapy components at reduced dose for current and subsequent cycles as specified below, at investigator's discretion and after approval by the Medical Monitor. • If immune etiology is unlikely and there is improvement to Grade ≤1, resume obinutuzumab/rituximab and atezolizumab at full dose and resume chemotherapy components at a reduced dose [a] for current and subsequent cycles as outlined below: –Atezo-G-CHOP or Atezo-R-CHOP: Decrease cyclophosphamide dose to 500 mg/m^2 and doxorubicin dose to 35 mg/m^2. –Atezo-G-benda: Decrease bendamustine dose to 70 mg/m^2. • Permanently discontinue study treatment for life-threatening liver toxicity.
	Grade 2 lasting >5–7 days	• Withhold atezolizumab. • 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, resume atezolizumab after corticosteroids have been tapered over ≥ 1 month to ≤ 10 mg/day of oral prednisone or equivalent. Contact Medical Monitor before resuming atezolizumab.

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

Event		Action to Be Taken
Amylase or lipase increase Grade ≥3 with or without abdominal pain	Grade ≥3	• Withhold study treatment. [a] • Investigate etiology. Consult with a gastroenterologist if immune etiology is suspected. • In cases of isolated increase of lipase or amylase that is asymptomatic and considered related to atezolizumab, obinutuzumab/rituximab and chemotherapy components treatment may be continued at current dose at the investigator's discretion and in discussion with the Medical Monitor. • Treat with corticosteroids following guidance provided in the Atezolizumab Investigator's Brochure. • If improvement to Grade ≤2 and patient is asymptomatic, resume obinutuzumab/rituximab at full dose and resume chemotherapy components at current dose. Atezolizumab may be resumed if approved by the Medical Monitor. Note: If pancreatitis is treated with corticosteroids, atezolizumab should not be resumed until the corticosteroids have been tapered to ≤10 mg/day of prednisone or equivalent. • Permanently discontinue atezolizumab for recurrent Grade 4 amylase/lipase elevations. For recurrent Grade 3 lipase or amylase increase that is isolated and asymptomatic, atezolizumab may be resumed following an individual benefit/risk assessment and in discussion with the Medical Monitor.
	Grade 2 long lasting (e.g., > 3 weeks)	• Continue study treatment. • Consider oral prednisone 10 mg daily or equivalent.
Ocular toxicity	Grade 3 or 4	• Withhold study treatment. [a] • Investigate etiology. Consult with an ophthalmologist. • Treat immune-related toxicity attributable to atezolizumab with systemic corticosteroids following guidance provided in the Atezolizumab Investigator's Brochure. • If improvement to Grade ≤1, resume obinutuzumab/rituximab at full dose and chemotherapy components at current dose. • Permanently discontinue atezolizumab.
	Grades 1 or 2	• Consult with an ophthalmologist. • Treat with topical corticosteroid eye drops. Topical immunosuppressive therapy may also be considered. • Discontinue atezolizumab if symptoms persist.

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 the Atezolizumab Investigator's Brochure for guidance on investigations in case of suspected immune-related colitis). • Treat with corticosteroids following guidance provided in the Atezolizumab Investigator's Brochure.
	Grade 2 or 3	• Withhold study treatment. [a] • Investigate etiology. Consult with a gastroenterologist if immune etiology is suspected (refer to the Atezolizumab Investigator's Brochure for guidance in case of suspected immune-related colitis). • Treat immune diarrhea/colitis with corticosteroids following guidance provided in the Atezolizumab Investigator's Brochure. • If diarrhea improves to Grade $\leq$1, resume obinutuzumab/rituximab at full dose and resume chemotherapy components at a reduced dose [a] for current and subsequent cycles as outlined below: –Atezo-G-CHOP or Atezo-R-CHOP: Decrease cyclophosphamide dose to 500 mg/m^2 and doxorubicin dose to 35 mg/m^2. – Atezo-G-benda: Decrease bendamustine dose to 70 mg/m^2. • If immune-related diarrhea/colitis improves to Grade $\leq$ 1 and any colitis has cleared as confirmed by sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, resume atezolizumab at full dose. Discuss with Medical Monitor before resuming atezolizumab. Note: If colitis is treated with corticosteroids, atezolizumab should not be resumed until the corticosteroids have been tapered to $\leq$10 mg/day of prednisone or equivalent.

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

Pulmonary event	Grades 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding a immunosuppressive agent. • 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] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • 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] • For recurrent events, treat as a Grade 3 or 4 event.
	Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.

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.[a] Permanently discontinue rituximab in the event of Stevens-Johnson syndrome or toxic epidermal necrolysis. • Investigate etiology. Consult with a dermatologist. A biopsy should be considered, unless contraindicated. • Administer oral prednisone 10 mg or equivalent. If event is unresolved after 48–72 hours, administer oral prednisone 60 mg or equivalent. • If improvement to Grade ≤1, resume obinutuzumab/rituximab at full dose and resume chemotherapy components at a reduced dose[a] for current and subsequent cycles as outlined below: – Atezo-G-benda: Decrease bendamustine dose to 70 mg/m^2. Atezolizumab may be resumed at full dose if rash is resolved and systemic corticosteroids dose is ≤10 mg/day of oral prednisone or equivalent. Discuss with the Medical Monitor before resuming atezolizumab. **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.

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

Event		Action to Be Taken
Hypothyroidism		• Investigate etiology. Consult with an endocrinologist (refer to the Atezolizumab Investigator's Brochure for guidance). • Start thyroid replacement hormone. • Monitor TSH weekly. <u>Asymptomatic elevation of TSH</u> • Continue study treatment. <u>Symptomatic elevation of TSH</u> • Withhold study treatment. [a] • If symptoms are controlled and TSH levels are decreasing, resume obinutuzumab/rituximab and atezolizumab at full dose and resume chemotherapy components at current dose. • Permanently discontinue atezolizumab for Grade ≥ 3 hypothyroidism.
Hypophysitis (panhypopituitarism)	Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • 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	• Withhold atezolizumab. • 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. • Resume atezolizumab if event resolves to Grade 1 or better, and patient is stable on replacement therapy (if required) within 12 weeks. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. • For recurrent hypophysitis, treat as a Grade 4 event.

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 < 0.5 mU/L or symptomatic patients • Withhold atezolizumab. • Consider consultation with an endocrinologist • Administer methimazole as needed. • Resume atezolizumab when symptoms are controlled by thyroid hormone replacement. • Permanently discontinue atezolizumab for life-threatening hyperthyroidism.
Hyperglycemia	Grade 3–4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Symptomatic adrenal insufficiency	Grade 2–4	• Withhold atezolizumab. • 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. • Resume atezolizumab if event resolves to Grade ≤ 1 and patient is stable on replacement therapy (if required) within 12 weeks. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. Contact the Medical Monitor before resuming atezolizumab.

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

Event		Action to Be Taken
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
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.
	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. • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.
	Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.

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

Event		Action to Be Taken
Other non-hematologic and non-immune-related toxicities (i.e., not described above), excluding alopecia, nausea, and vomiting	Grade 3 or 4	**For patients who have had no prior chemotherapy dose reductions:** • Withhold study treatment . [a] • If improvement to Grade ≤1 or baseline, resume obinutuzumab/rituximab and atezolizumab at full dose and resume chemotherapy components at a reduced dose [a] for current and subsequent cycles as outlined below: – Atezo-G-CHOP or Atezo-R-CHOP: Decrease cyclophosphamide dose to 500 mg/m^2 and doxorubicin dose to 35 mg/m^2. – Atezo-G-benda: Decrease bendamustine dose to 70 mg/m^2. **For patients who have had one prior chemotherapy dose reduction:** <u>Grade 4 events</u> • Permanently discontinue study treatment. <u>Grade 3 events</u> • Withhold study treatment. [a] • If improvement to Grade ≤1 or baseline, resume obinutuzumab/rituximab and atezolizumab at full dose and resume chemotherapy components at a reduced dose [a] for subsequent cycles as outlined below: – Atezo-G-CHOP or Atezo-R-CHOP: Decrease cyclophosphamide dose to 375 mg/m^2 and doxorubicin dose to 25 mg/m^2. – Atezo-G-benda: Decrease bendamustine dose to 50 mg/m^2. No more than two dose reductions of chemotherapy are allowed. **For patients who have had two prior chemotherapy dose reductions:** • Permanently discontinue study treatment.
	Grade 2	• Withhold study treatment. [a] • If there is improvement to Grade ≤1 or baseline, resume obinutuzumab/rituximab and atezolizumab at full dose and resume chemotherapy components at current dose.

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

Atezo = atezolizumab; benda = bendamustine; BAL = bronchoscopic alveolar lavage; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CT = computed tomography; DBLCL = diffuse large B-cell lymphoma; ECMO = extracorporeal membrane oxygenation; FL = follicular lymphoma; G = obinutuzumab; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; LMWH = low-molecular-weight heparin; MRI = magnetic resonance imaging; NHL = non-Hodgkin's lymphoma; PML = progressive multifocal leukoencephalopathy; R = rituximab; TSH = thyroid-stimulating hormone; VAD = ventricular assist device.

[a] Treatment delays apply to all events; dose modifications apply only to events that are considered to be related to any of the study treatment components. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications. For Grade 3 laboratory abnormalities that are isolated, asymptomatic and considered not clinically significant, study treatment may be either continued or resumed at the current dose upon improvement to Grade 2, at the investigator's discretion, following an individual benefit/risk assessment. For Grade 2 isolated and asymptomatic laboratory abnormalities, study treatment may be continued at the current dose.

[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 $\leq$10 mg/day oral prednisone or equivalent. 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 $\geq$1 month to $\leq$10 mg/day oral prednisone or equivalent 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 Consolidation or Maintenance Treatment

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

Table 15 Guidelines for Management of Toxicities That Occur during Consolidation or Maintenance Treatment

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

G-CSF = granulocyte colony-stimulating factor.

[a] Treatment delays apply to all events; dose modifications apply only to events that are considered to be related to any of the study treatment components. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study 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 criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

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

Events for which additional data collection will be required are PML, 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 serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study 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 serious adverse events that are believed to be related to prior study treatment (see Section 5.6).

An exception is made for Grade 3–4 infections (related and unrelated to study treatment), which should be reported until up to 2 years after the last dose of obinutuzumab (in the Atezo-G-benda and Atezo-G-CHOP treatment groups).

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. 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 or not 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 decrease 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 serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should 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 × baseline value) in combination with either an elevated total bilirubin (>2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

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

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of 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").

During survival follow-up, deaths attributed to progression of lymphoma should be recorded only on the Study Completion/Early Discontinuation eCRF.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Lymphoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should **not** be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the Lugano 2014 criteria (see Appendix 7) and the modified Cheson 2007 criteria (see Appendix 8). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study 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. Additionally, 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:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 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 serious adverse events 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 and Adverse Events of Special Interest

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 serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment. 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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting 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 and for at least 18 months after the last dose of study treatment for patients in the Atezo-G-benda and Atezo-G-CHOP treatment groups and for at least 12 months after the last dose of study treatment for patients in the Atezo-R-CHOP 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 immediately and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus.

Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 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 serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 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 serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study 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 serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, 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 treatment, the event should be reported through use of the Adverse Event eCRF.

An exception is made for Grade 3–4 infections (related and unrelated), 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, even if the Atezo-G-benda 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 serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

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

- Obinutuzumab Investigator's Brochure
- Atezolizumab Investigator’s Brochure
- Rituximab Investigator’s Brochure
- Bendamustine Summary of Product Characteristics

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 safety run-in phase followed by an expansion phase. During the safety run-in phase, 6 patients with previously untreated, or relapsed or refractory FL are to be enrolled within each treatment group (Atezo-G-CHOP or Atezo-G-benda). If the stopping criteria are not met during the safety run-in phase within a treatment group, enrollment will continue in the expansion phase, as follows:

- Additional patients with previously untreated FL will be enrolled in the Atezo-G-benda treatment group.

- Patients with previously untreated DLBCL will be enrolled in the Atezo-R-CHOP treatment group.

Enrollment in the Atezo-G-CHOP treatment group was stopped after the safety run-in phase was completed.

6.1 DETERMINATION OF SAMPLE SIZE

Up to 46 patients with FL will be enrolled in the Atezo-G-benda treatment group: 6 patients with previously untreated, or relapsed or refractory FL enrolled in the safety run-in phase and 34–40 patients with previously untreated FL enrolled in the expansion phase (depending on the number of patients needed to achieve a total enrollment of 40 patients with previously untreated FL). A total of 7 patients with previously untreated or relapsed or refractory FL were enrolled in the Atezo-G-CHOP treatment group during the safety run-in phase. Per current amendment, , further enrollment in the Atezo-G-CHOP treatment group is stopped. A total of 40 patients with previously untreated DLBCL will be enrolled in the Atezo-R-CHOP treatment group. Therefore, enrollment of up to 92 patients is planned for this 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.

Data from completed and ongoing studies in similar disease settings will be used as historical controls for comparison. Currently available data indicate that the historical CR rate is approximately 40% for first-line treatment of FL (Dyer et al. 2012; Rummel et al. 2013) and 59% for first-line treatment of DLBCL (Study BO21005/GOYA), as assessed by Cheson 2007 criteria. A sample size of 40 patients is deemed sufficient to provide adequate precision for the point estimate and for the lower bound of the two-sided 90% CI to rule out a clinically uninteresting probability of response of $<$40% in FL and $<$59% in DLBCL, assuming an observed PET-CT–defined CR rate of 55% and 72%, respectively. Updated estimates of the proportion of patients expected to achieve a PET-CT–defined CR for each histological subtype are expected to be available from ongoing studies by the time of the first interim analysis and will be used as reference data.

Table 17 lists the two-sided 90% Clopper-Pearson exact CI for the true probability of achieving a PET-CT–defined CR at EOI for a range of observed proportions based on a sample of 40 patients.

Table 17 Potential 90% CI for the True Probability of Achieving a PET-CT–Defined Complete Response at End of Induction

Observed Proportion of Patients Achieving a PET-CT–Defined CR at EOI	Two-Sided 90% Clopper-Pearson CI [a] for True Population PET-CT–Defined CR
0.50	(0.36, 0.64)
0.55	(0.40. 0.68)
0.60	(0.46, 0.73)
0.65	(0.51, 0.77)
0.70	(0.56, 0.82)
0.72	(0.58, 0.83)
0.75	(0.61, 0.86)
0.80	(0.66, 0.89)
0.85	(0.72, 0.93)

CR = complete response; CT = computed tomography; EOI = end of induction; PET = positron emission tomography.

[a] Note that the lower limit of a two-sided 90% CI is equivalent to a one-sided 95% CI.

6.2 SUMMARIES OF PATIENT CHARACTERISTICS

Summaries of patient characteristics will be performed by treatment group. 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 for each treatment group using descriptive statistics (mean, standard deviation, median, and range).

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics, 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.

6.4 SAFETY ANALYSES

The safety analyses will be performed by treatment group, separately for each treatment phase (i.e., safety run-in and expansion), and will include all treated patients (i.e., patients who received any amount of study treatment), with patients grouped according to treatment received.

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

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

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

Relevant laboratory and vital sign (temperature, heart rate, respiratory rate, and blood pressure) data will be displayed by time, with Grade 3 and 4 values identified as appropriate.

6.5 EFFICACY ANALYSES

The primary and secondary efficacy analyses will be performed by treatment group, with patients grouped according to treatment received. For the Atezo-R-CHOP treatment group, the efficacy analyses will include all patients enrolled in the expansion phase. For the Atezo-G-benda treatment group, the efficacy analyses will include all patients enrolled in the expansion phase as well as patients with previously untreated FL who were enrolled in the safety run-in phase.

Response will be determined through use of the modified Cheson 2007 criteria (Cheson et al. 2007; see Appendix 8), which take into account both PET-CT and CT scan results, and through use of the PET-CT–based Lugano 2014 criteria (Cheson et al. 2014; see Appendix 7).

6.5.1 Primary Efficacy Endpoint

The primary efficacy analysis will be estimation of the proportion of patients achieving a CR at EOI, as determined by the IRC through use of the PET-CT–based Lugano 2014 criteria. Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. The primary efficacy analysis will include patients who received at least one dose of atezolizumab. Patients without a post-baseline tumor assessment will be considered non-responders.

6.5.2 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 using Lugano 2014 criteria
- CR at EOI, as determined by the IRC and by the investigator using modified Cheson 2007 criteria

- Objective response (defined as a CR or PR) at EOI, as determined by the IRC and by the investigator using Lugano 2014 criteria and modified Cheson 2007 criteria
- Objective response (defined as a CR or PR) during the study, as determined by the investigator using modified Cheson 2007 criteria

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.

6.5.3 Exploratory Efficacy Endpoints

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

- For patients who have positive PET scans at EOI: CR at 12 months, as determined by the IRC and by the investigator using Lugano 2014 criteria
- CR at 12, 24, and 30 months in patients with previously untreated FL, as determined by the investigator using modified Cheson 2007 criteria

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.

Exploratory efficacy analyses will also be performed on the following endpoints:

- PFS
- EFS
- DFS
- OS

PFS, EFS, DFS, and OS will be summarized descriptively using the Kaplan-Meier method (Kaplan and Meier 1958). For the PFS, EFS, and DFS analyses, data for patients without an event of interest will be censored at the date of the last tumor assessment. For patients without post-baseline tumor assessments, data will be censored at the date of initiation of study treatment plus 1. 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). In addition, landmark estimates of the proportion of patients who are event free at 6 months, 9 months, 1 year, and 2 years will be provided, along with 95% asymptotic CIs using Greenwood's formula for standard errors. No formal comparison of time-to-event outcomes by treatment group will be conducted.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum concentrations of obinutuzumab-, rituximab-, and atezolizumab-versus-time data will be tabulated and plotted, after appropriate grouping. After appropriate grouping, summary statistics of concentration data will be computed for each scheduled sampling time for each analyte, and interpatient variability and drug accumulation after multiple doses will be evaluated. Compartmental, non-compartmental, and/or population approaches will be considered as appropriate, including potential pooled analyses across studies. Potential drug interactions may be assessed by comparison of pharmacokinetics in the current study with historical data. Potential correlations between PK variability and demographic and pathophysiological covariates may be explored by population PK analysis. Potential correlations between PK variability and pharmacodynamic (PD), efficacy, and safety endpoints may be explored by exploratory graphical analysis and PK/PD modeling. The assessment of PK parameters and related analyses will be performed per the Sponsor's discretion, taking into consideration the appropriateness of the PK data collected and the trial outcome. Compartmental and/or population PK/PD analyses may be reported separately from CSR.

6.7 IMMUNOGENICITY ANALYSES

The numbers and proportions of HAHA-, HACA-, or ATA-positive patients HAHA-, HACA-, or ATA-negative patients during both the treatment and follow-up periods will be summarized by treatment group.

The relationship between HAHA, HACA, or ATA status and safety, efficacy, and PK endpoints will be explored as appropriate.

6.8 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 for each treatment group with respect to both IRC- and 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.

6.9 INTERIM ANALYSES

It is anticipated that at least one interim analysis will be conducted during the expansion phase of the study, when at least 15 patients have been evaluated for PET-CT-defined CR at the EOI. Additional analyses may be conducted to guide early stopping of enrollment for safety on the basis of observed toxicities and the ability to maintain chemotherapy dose intensity.

During the expansion phase, a modified version of the predictive probability design (Lee and Liu 2008) may be used to guide early stopping for futility by comparing the observed proportion of patients who achieve a PET-CT–defined CR at EOI in each expansion cohort with that in historical controls. The earliest interim analysis would occur after at least 15 patients have been evaluated for PET-CT–defined CR at EOI.

If, at any time, an interim analysis suggests that the proportion of patients achieving a PET-CT–defined CR for one of the expansion cohorts is lower or higher than expected, the IMC will review the data and decide whether to recommend an early decision to stop enrollment in that subgroup. Interim analysis decision rules will be based on the modified version of the predictive probability that the trial will have a positive outcome if carried out to completion and will use the historical control data available at the time of analysis.

Additional 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 document.

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.

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

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

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

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

7.3 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, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records 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 GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

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 of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the 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 FL patients have completed or discontinued study treatment and all enrolled DLBCL patients 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 Roche.

Electronic data capture will be used for this study. An IxRS will be used to assign patient numbers. A central laboratory will be used for a subset of laboratory assessments as specified in Section 4.5.6; otherwise, local laboratories will be used. A central independent review facility will be used to collect PET-CT and CT scans, and the IRC will perform independent assessments of response for all patients enrolled in the study (separate IRC Charter will contain all details). Data from this study will be shared with an Expert Scientific Committee that will provide scientific input for the benefit-risk assessment for each combination.

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 in the Atezo-G-Benda Treatment Group

	Screening [a]		Induction (6 months; 28-day cycles)							EOI	Maint. (24 months)		EOM [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
	D −28 to D −1	D −14 to D −1	Cycle 1 (±1 d)			Cycle 2 (±2 d)		Cycles 3–6 (±2 d)		After last induction dose [b]	Monthly (±1 wk)	Every 2 months (±1 wk)	35 days after last dose		
			D1	D8	D15	D1	D15	D1	D15		D1	D1			
Informed consent [e]	x														
Demographic data	x														
Medical history	x														
ECOG Performance Status	x														
Vital signs [f]	x		x	x	x	x	x	x	x	x [g]	x [mm]	x	x		
Height	x														
Weight and body surface area	x														
12-lead ECG	x									x [g]			x		
Complete physical examination [h, i]	x														
Targeted physical examination [i, j]			Cycles 2 and 4							x		x	x	x	
Ann Arbor, FLIPI, and FLIPI2	x														
B symptoms [k]	x									x	x [l]		x [m]	x [n]	
β_2 microglobulin			x												
Hematology [o]		x	x [p,q]	x [q]	x [q]	x [q]	x	x [q]	x	x [g]	x [mm]	x	x		
Serum chemistry [r]		x	x [p,q]	x [q]	x [q]	x [q]	x	x [q]	x	x [g]	x [mm]	x	x		
Coagulation (INR, aPTT [or PTT], and PT)		x													
Pregnancy test [s]		x								x [g]			x		

Appendix 1
Schedule of Assessments for Patients in the Atezo-G-Benda Treatment Group (cont.)

	Screening [a]		Induction (6 months; 28-day cycles)							EOI	Maint. (24 months)		EOM [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
	D −28 to D −1	D −14 to D −1	Cycle 1 (±1 d)			Cycle 2 (±2 d)		Cycles 3–6 (±2 d)		After last induction dose [b]	Monthly (±1 wk)	Every 2 months (±1 wk)	35 days after last dose		
			D1	D8	D15	D1	D15	D1	D15		D1	D1			
Hepatitis B and C testing [t]	x														
Quantitative IgA, IgG, IgM			x							x	x [l]		x	x [u]	
TSH, T3, T4		x	Every 3 months												
HAHA sample for obinutuzumab			x [v]												
ATA sample for atezolizumab			x [v]												
PK sample for obinutuzumab			x [v]												
PK sample for atezolizumab			x [v]												
Serum for soluble PD-L1			x												
Whole blood for MRD [w]			x [q]							x	x [l]				
Whole blood for lymphocyte immunophenotyping [x]			x [q]		x [q]	x [q]		x [q]		x	x [l]		x	x [u]	
Whole blood for T-cell receptor repertoire in PBMCs			x [q]			x [q]		x [q, y]		x	x [z]				
Serum for cytokine analysis			x [q]			x [q]		x [q, y]							
Optional peripheral blood sample for RCR [aa]			x												

Appendix 1
Schedule of Assessments for Patients in the Atezo-G-Benda Treatment Group (cont.)

		Screening [a]		Induction (6 months; 28-day cycles)							EOI	Maint. (24 months)		EOM [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
		D −28 to D −1	D −14 to D −1	Cycle 1 (±1 d)			Cycle 2 (±2 d)		Cycles 3–6 (±2 d)		After last induction dose [b]	Monthly (±1 wk)	Every 2 months (±1 wk)	35 days after last dose		
				D1	D8	D15	D1	D15	D1	D15		D1	D1			
Tumor tissue specimen (leftover tissue may be used for optional RCR specimen [aa])		x [bb]					x [cc]				x [cc]					
Concomitant medications		x		To be recorded continually until end of treatment												
Adverse events [dd]		x		To be assessed continually [dd]												
PET-CT scan		x [ee]									x [ff]	x [gg]				
CT scan [hh]		x [hh]									x [ff]	x [ii]		x [m]	x [n]	
Bone marrow biopsy and aspirate		x [jj]									x [ff, kk]	x [kk]		x [m, kk]		
Study treatment administration	Obinutuzumab [ll]			x	x	x	x		x				x			
	Atezolizumab [ll]						D1, D15		D1, D15			D1, D2				
	Bendamustine [ll]			D1, D2			D1, D2		D1, D2							
New anti-lymphoma treatment															x	x
Survival follow-up																x

ATA = anti-therapeutic antibody; Atezo-G-benda = atezolizumab in combination with obinutuzumab plus bendamustine; CT = computed tomography; D = day; Discont. = discontinuation; 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; Ig = immunoglobulin; Maint. = maintenance; MRD = minimal residual disease; MRI = magnetic resonance imaging; NK = natural killer; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed death–ligand 1; PET = positron emission tomography; PK = pharmacokinetic; q3m = every 3 months; RCR = Roche Clinical Repository; wk = week.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Appendix 1
Schedule of Assessments for Patients in the Atezo-G-Benda Treatment Group (cont.)

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 maintenance treatment or discontinue maintenance treatment prematurely will undergo assessments at EOM.

[d] Patients who complete treatment or discontinue treatment for reasons other than disease progression will undergo assessments every 3 months during the post-treatment FU period, which will continue until disease progression, the start of new anti-lymphoma treatment, or the end of the study, whichever occurs first. The first post-treatment FU visit is 3 months after the EOI visit for patients who do not receive maintenance treatment and 3 months after the last dose for patients who receive maintenance treatment. Patients who experience disease progression will undergo limited assessments every 3 months during the survival FU period, which will continue until the end of the study. The end of the study is defined as the time when all enrolled FL patients have completed or discontinued study treatment and all enrolled DLBCL patients have been followed for at least 1 year after they have completed or discontinued study treatment.

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

[f] Vital signs include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. For obinutuzumab infusions: For the first 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 the second and 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 atezolizumab infusions: Vital signs should be determined up to 60 (±15) minutes before each atezolizumab infusion. Vital signs should also be obtained during or after the atezolizumab infusion if clinically indicated.

[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, unexplained weight loss > 10% of body weight over 6 months.

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

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

[n] Perform every 6 months.

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

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

[q] Perform hematology and chemistry tests within 72 hours prior to Day 1 of each cycle, and within 24 hours prior to Days 8 and 15 of Cycle 1. Samples for exploratory biomarker research should be collected at the same time as hematology and chemistry samples.

[r] Includes sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, amylase, lipase, LDH, and uric acid.

[s] All women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days prior to Day 1 of Cycle 1.

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

[u] Perform every 3 months until disease progression, or the start of new anti-lymphoma treatment, whichever occurs first.

[v] See Appendix 4 for detailed schedule.

[w] Includes circulating lymphoma cells and/or cell-free circulating tumor DNA.

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

[y] Cycle 3 only.

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

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

[bb] Availability of adequate archival or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.6 for details).

[cc] 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.

[dd] 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 3–4 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.

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

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

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

[hh] 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. Screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[ii] Perform at 12, 18, and 24 months after initiation of induction treatment, within 14 days prior to treatment administration.

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

[kk] 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).

[ll] Refer to Sections 4.3.2.6 and 4.3.2.8 for details on dosing and schedule.

[mm] Patient may be assessed every 2 months if atezolizumab has been discontinued and maintenance treatment is continued with obinutuzumab single agent.

Appendix 2
Schedule of Assessments for Patients with FL in the Atezo-G-CHOP Treatment Group

	Screening [a]		Induction (4 months; 21-day cycles)					EOI	Maint. (24 months)		EOM [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
	D −28 to D −1	D −14 to D −1	Cycle 1 (±1 d)			Cycle 2 (±2 d)	Cycles 3–6 (±2 d)	After last induction dose [b]	Monthly (±1 wk)	Every 2 months (±1 wk)	35 days after last dose		
			D1	D8	D15	D1	D1		D1	D1			
Informed consent [e]	x												
Demographic data	x												
Medical history	x												
ECOG Performance Status	x												
Vital signs [f]	x		x	x	x	x	x	x [g]	x [mm]	x	x		
Height	x												
Weight and body surface area	x												
12-lead ECG	x							x [g]			x		
LVEF (echocardiography or MUGA scan)	x												
Complete physical examination [h, i]	x												
Targeted physical examination [l, j]			Cycles 2 and 4					x		x	x	x	
Ann Arbor, FLIPI, and FLIPI2	x												
B symptoms [k]	x							x	x [l]		x [m]	x [n]	
β_2 microglobulin			x										
Hematology [o]		x	x [p,q]	x [q]	x [q]	x [q]	x [q]	x [g]	x [mm]	x	x		
Serum chemistry [r]		x	x [p,q]	x [q]	x [q]	x [q]	x [q]	x [g]	x [mm]	x	x		

Appendix 2
Schedule of Assessments for Patients with FL in the Atezo-G-CHOP Treatment Group (cont.)

	Screening [a]		Induction (4 months; 21-day cycles)					EOI	Maint. (24 months)		EOM [c] 35 days after last dose	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
	D −28 to D −1	D −14 to D −1	Cycle 1 (±1 d)			Cycle 2 (±2 d)	Cycles 3–6 (±2 d)	After last induction dose [b]	Monthly (±1 wk)	Every 2 months (±1 wk)			
			D1	D8	D15	D1	D1		D1	D1			
Coagulation (INR, aPTT [or PTT], and PT)		x											
Pregnancy test [s]		x						x [g]			x		
Hepatitis B and C testing [t]	x												
Quantitative IgA, IgG, IgM			x					x	x [l]		x	x [u]	
TSH, T3, T4		x	Every 3 months										
HAHA sample for obinutuzumab			x [v]										
ATA sample for atezolizumab (MPDL3280A)			x [v]										
PK sample for obinutuzumab			x [v]										
PK sample for atezolizumab (MPDL3280A)			x [v]										
Serum for soluble PD-L1			x										
Whole blood for MRD [w]			x [q]					x	x [l]				
Whole blood for lymphocyte immunophenotyping [x]			x [q]		x [q]	x [q]	x [q]	x	x [l]		x	x [u]	
Whole blood for T-cell receptor repertoire in PBMCs			x [q]			x [q]	x [q,y]	x	x [z]				
Serum for cytokine analysis			x [q]			x [q]	x [q,y]						
Optional peripheral blood sample for RCR [aa]			x										

Appendix 2
Schedule of Assessments for Patients with FL in the Atezo-G-CHOP Treatment Group (cont.)

		Screening [a]		Induction (4 months; 21-day cycles)					EOI	Maint. (24 months)		EOM [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
		D −28 to D −1	D −14 to D −1	Cycle 1 (±1 d)			Cycle 2 (±2 d)	Cycles 3–6 (±2 d)	After last induction dose [b]	Monthly (±1 wk)	Every 2 months (±1 wk)	35 days after last dose		
				D1	D8	D15	D1	D1		D1	D1			
Tumor tissue specimen (leftover tissue may be used for optional RCR specimen [aa])		x [bb]					x [cc]		x [cc]					
Concomitant medications		x		To be recorded continually until end of treatment										
Adverse events [dd]		x		To be assessed continually [dd]										
PET-CT scan		x [ee]							x [ff]	x [gg]				
CT scan [hh]		x [hh]							x [ff]	x [ii]		x [m]	x [n]	
Bone marrow biopsy and aspirate		x [jj]							x [ff,kk]	x [kk]		x [m,kk]		
Study treatment administration	Obinutuzumab [ll]			x	x	x	x	x			x			
	Atezolizumab [ll]						x	x		D1, D2				
	CHOP [ll]			D1–5 of Cycles 1–6										
New anti-lymphoma treatment													x	x
Survival follow-up														x

ATA = anti-therapeutic antibody; Atezo-G-CHOP = atezolizumab in combination with obinutuzumab plus CHOP; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CT = computed tomography; D = day; Discont. = discontinuation; 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; LVEF = left ventricular ejection fraction; Maint. = maintenance; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NK = natural killer; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed death–ligand 1; PET = positron emission tomography; PK = pharmacokinetic; q3m = every 3 months; RCR = Roche Clinical Repository; 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).

Appendix 2
Schedule of Assessments for Patients with FL in the Atezo-G-CHOP Treatment Group (cont.)

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[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 maintenance treatment or discontinue maintenance treatment prematurely will undergo assessments at EOM.

[d] Patients who complete treatment or discontinue treatment for reasons other than disease progression will undergo assessments every 3 months during the post-treatment FU period, which will continue until disease progression, the start of new anti-lymphoma treatment, or the end of the study, whichever occurs first. The first post-treatment FU visit is 3 months after the EOI visit for patients who do not receive maintenance treatment and 3 months after the last dose for patients who receive maintenance treatment. Patients who experience disease progression will undergo limited assessments every 3 months during the survival FU period, which will continue until the end of the study. The end of the study is defined as the time when all enrolled FL patients have completed or discontinued study treatment and all enrolled DLBCL patients have been followed for at least 1 year after they have completed or discontinued study treatment.

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

[f] Vital signs include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. For obinutuzumab infusions: For the first cycle and for patients who experience an infusion-related reaction, vital signs will be measured prior to the infusion, every 15 ($\pm$5) minutes for the first 90 minutes of the infusion, and then every 30 ($\pm$10) minutes until 1 hour after completion of the infusion. For the second and subsequent cycles, vital signs will be measured every 30 minutes during the infusion, except in patients who had experienced an infusion-related reaction during a prior infusion. For atezolizumab infusions: Vital signs should be determined up to 60 ($\pm$15) minutes before each atezolizumab infusion. Vital signs should also be obtained during or after the atezolizumab infusion if clinically indicated.

[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, unexplained weight loss $>$10% of body weight over 6 months.

Appendix 2
Schedule of Assessments for Patients with FL in the Atezo-G-CHOP Treatment Group (cont.)

[l] Perform at the same time as tumor assessments at 12, 18, and 24 months after initiation of induction treatment.
[m] Perform only if not done within the previous 3 months.
[n] Perform every 6 months.
[o] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
[p] Screening laboratory assessments may be used for Day 1 of Cycle 1 if performed within 72 hours prior to Day 1 of Cycle 1.
[q] Perform hematology and chemistry tests within 72 hours prior to Day 1 of each cycle, and within 24 hours prior to Days 8 and 15 of Cycle 1. Samples for exploratory biomarker research should be collected at the same time as hematology and chemistry samples.
[r] Includes sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, amylase, lipase, LDH, and uric acid.
[s] All women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days prior to Day 1 of Cycle 1.
[t] Includes hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody.
[u] Perform every 3 months until disease progression, or the start of new anti-lymphoma treatment, whichever occurs first.
[v] See Appendix 5 for detailed schedule.
[w] Includes circulating lymphoma cells and/or cell-free circulating tumor DNA.
[x] Includes B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK-cell counts (CD16 and CD56).
[y] Cycle 3 only.
[z] Perform at the same time as tumor assessments at 12 and 18 months after initiation of induction treatment.
[aa] Requires separate patient consent for RCR participation. Not applicable for a site that has not been granted approval for RCR sampling.
[bb] Availability of adequate archival or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.6 for details).
[cc] 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.
[dd] 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 3–4 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.
[ee] The screening PET-CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

[ff] Perform only for patients who have received at least two cycles of induction treatment.
[gg] If PET-CT scan is positive at EOI, perform at 12 months after initiation of induction treatment, within 14 days prior to treatment administration.
[hh] 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. Screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.
[ii] Perform at 12, 18, and 24 months after initiation of induction treatment, within 14 days prior to treatment administration.
[jj] Bone marrow biopsy and aspirate must be performed within approximately 3 months prior to Day 1 of Cycle 1.
[kk] 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).
[ll] Refer to Sections 4.3.2.7 and 4.3.2.8 for details on dosing and schedule.
[mm] Patient may be assessed every 2 month if atezolizumab has been discontinued and maintenance treatment is continued with obinutuzumab single agent.

Appendix 3
Schedule of Assessments for Patients with DLBCL in the Atezo-R-CHOP Treatment Group

	Screening [a]		Induction (6 months; 21-day cycles)			EOI	Consolidation (21-day cycles)	EOC [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
	D –28 to D –1	D –14 to D –1	Cycle 1 (±1 d)	Cycle 2 (±2 d)	Cycles 3–8 (±2 d)	After last induction dose [b]	Cycles 9–25 (± 3 days)	35 days after last dose		
			D1	D1	D1		D1			
Informed consent [e]	x									
Demographic data	x									
Medical history	x									
ECOG Performance Status	x									
Vital signs [f]	x		x	x	x	x [g]	x	x		
Height	x									
Weight and body surface area	x									
12-lead ECG	x					x [g]		x		
LVEF (echocardiography or MUGA scan)	x									
Complete physical examination [h, i]	x									
Targeted physical examination [i, j]			Cycles 2, 4, and 6			x	Every 2 cycles	x	x	
Ann Arbor staging, IPI	x									
B symptoms [k]	x					x	Within 1 week prior to C17	x [l]	x [m]	
β_2 microglobulin			x							
Hematology [n]		x	x [o,p]	x [p]	x [p]	x [g]	x	x		
Serum chemistry [q]		x	x [o,p]	x [p]	x [p]	x [g]	x	x		

Appendix 3
Schedule of Assessments for Patients with DLBCL in the Atezo-R-CHOP Treatment Group (cont.)

	Screening [a]		Induction (6 months; 21-day cycles)			EOI	Consolidation (21-day cycles)	EOC [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
	D −28 to D −1	D −14 to D −1	Cycle 1 (± 1 d)	Cycle 2 (± 2 d)	Cycles 3–8 (± 2 d)	After last induction dose [b]	Cycles 9–25 (± 3 days)	35 days after last dose		
			D1	D1	D1		D1			
Coagulation (INR, aPTT [or PTT], and PT)		x								
Pregnancy test [r]		x				x [g]		x		
Hepatitis B and C testing [s]	x									
Quantitative IgA, IgG, IgM			x			x		x	x	
TSH, T3, T4		x	Every 3 months							
HACA sample for rituximab			x [t]							
ATA sample for atezolizumab (MPDL3280A)			x [t]							
PK sample for rituximab			x [t]							
PK sample for atezolizumab (MPDL3280A)			x [t]							
Serum for soluble PD-L1			x							
Whole blood for MRD [u]			x [p]			x	Within 1 week prior to C17	x	x	
Whole blood for lymphocyte immunophenotyping [v]			x [p]	x [p]	x [p]	x	Within 1 week prior to C17	x	x	
Whole blood for T-cell receptor repertoire in PBMCs			x [p]	x [p]	x [p, w]	x	Within 1 week prior to C17	x	x	

Appendix 3
Schedule of Assessments for Patients with DLBCL in the Atezo-R-CHOP Treatment Group (cont.)

		Screening [a]		Induction (6 months; 21-day cycles)			EOI	Consolidation (21-day cycles)	EOC [c]	Post-Treatment FU Period (q3m) [d]	Survival FU Period (q3m) [d]
		D −28 to D −1	D −14 to D −1	Cycle 1 (±1 d)	Cycle 2 (±2 d)	Cycles 3–8 (±2 d)	After last induction dose [b]	Cycles 9–25 (± 3 days)	35 days after last dose		
				D1	D1	D1		D1			
Serum for cytokine analysis				x [p]	x [p]	x [p, w]					
Optional peripheral blood sample for RCR [x]				x							
Tumor tissue specimen (leftover tissue may be used for optional RCR specimen [x])		x [y]			x [z]		x [z]				
Concomitant medications		x		To be recorded continually until end of treatment							
Adverse events [aa]		x		To be recorded continually [aa]							
PET-CT scan		x [bb]					x [cc]				
CT scan [dd]		x [dd]					x [cc]	Within 1 week prior to C17	x [l]	x [m]	
Bone marrow biopsy and aspirate		x [ee]					x [cc, ff]	x [ff]	x [l, ff]		
Study treatment administration	Rituximab [gg]			x	x	x					
	Atezolizumab [gg]				x	x		x			
	CHOP [gg]			D1–5	D1–5 of Cycles 2–6/8						
New anti-lymphoma treatment										x	x
Survival follow-up											x

Appendix 3
Schedule of Assessments for Patients with DLBCL in the Atezo-R-CHOP Treatment Group (cont.)

ATA = anti-therapeutic antibody; Atezo-R-CHOP = atezolizumab in combination with rituximab plus CHOP; C = cycle; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CT = computed tomography; D = day; Discont. = discontinuation; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOC = end of consolidation; EOI = end of induction; FU = follow-up; HAHA = human anti-human antibody; IPI = International Prognostic Index; LVEF = left ventricular ejection fraction; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NK = natural killer; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed death–ligand 1; PET = positron emission tomography; PK = pharmacokinetic; q3m = every 3 months; RCR = Roche Clinical Repository; 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 consolidation treatment or discontinue consolidation treatment prematurely will undergo assessments at EOC.

[d] Patients who complete treatment or discontinue treatment for reasons other than disease progression will undergo assessments every 3 months during the post-treatment FU period, which will continue until disease progression, the start of new anti-lymphoma treatment, or the end of the study, whichever occurs first. The first post-treatment FU visit is 3 months after the EOI visit for patients who do not receive consolidation treatment and 3 months after the last dose for patients who receive consolidation treatment. Patients who experience disease progression will undergo limited assessments every 3 months during the survival FU period, which will continue until the end of the study. The end of the study is defined as the time when all enrolled FL patients have completed or discontinued study treatment and all enrolled DLBCL patients have been followed for at least 1 year after they have completed or discontinued study treatment.

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

[f] Vital signs include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. For rituximab infusions: Vital signs monitoring during infusion should be determined as per local label. For atezolizumab infusions: Vital signs should be determined up to 60 (±15) minutes before each atezolizumab infusion. Vital signs should also be obtained during or after the atezolizumab infusion if clinically indicated.

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

Appendix 3
Schedule of Assessments for Patients with DLBCL in the Atezo-R-CHOP Treatment Group (cont.)

[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, unexplained weight loss $>10\%$ of body weight over 6 months.

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

[m] Perform every 6 months.

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

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

[p] Perform hematology and chemistry tests within 72 hours prior to Day 1 of each cycle 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.

[q] Includes sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, amylase, lipase, LDH, and uric acid.

[r] All women who are not postmenopausal ($\geq$12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days prior to Day 1 of Cycle 1.

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

[t] See Appendix 6 for detailed schedule.

[u] Includes circulating lymphoma cells and/or cell-free circulating tumor DNA.

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

[w] Cycle 3 only.

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

[y] Availability of adequate archival or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.6 for details).

[z] 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.

[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). 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] 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. Screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.

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

[ff] 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 consolidation and at EOC if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression).

[gg] Refer to Sections 4.3.2.7 and 4.3.2.8 for details on dosing and schedule.

Appendix 4
Pharmacokinetic and Immunogenicity Sampling Schedule for the Atezo-G-Benda Treatment Group

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	Serum Atezolizumab Pharmacokinetic Sample	Serum Obinutuzumab HAHA Sample	Serum Atezolizumab ATA Sample
Induction (Cycle 1 to Cycle 6; 28-day cycles)					
Cycle 1	Day 1	Prior to obinutuzumab infusion (any time prior to dose); After obinutuzumab infusion [b] (30 min [± 10 min] after end of infusion)	—	Prior to obinutuzumab infusion (any time prior to dose)	—
Cycle 2	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose); After atezolizumab infusion (30 min [± 10 min] after end of infusion)	—	Prior to atezolizumab infusion (any time prior to dose)
	Day 15	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	—
Cycle 3	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)
	Day 15	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)
Cycle 5	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	Prior to obinutuzumab infusion (any time prior to dose)	Prior to atezolizumab infusion (any time prior to dose)

Appendix 4
Pharmacokinetic and Immunogenicity Sampling Schedule for the Atezo-G-Benda Treatment Group (cont.)

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	Serum Atezolizumab Pharmacokinetic Sample	Serum Obinutuzumab HAHA Sample	Serum Atezolizumab ATA Sample
Induction (Cycle 1 to Cycle 6; 28-day cycles)					
End of Induction (Cycle 6)	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	Prior to obinutuzumab infusion (any time prior to dose)	Prior to atezolizumab infusion (any time prior to dose)
Maintenance (Month 1 to Month 24)					
Month 1	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	Prior to obinutuzumab infusion (any time prior to dose)	Prior to atezolizumab infusion (any time prior to dose)
Month 2	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose); After atezolizumab infusion (30 min [± 10 min] after end of infusion)	—	—
Month 3	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	—	—	—
Month 4	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)

Appendix 4
Pharmacokinetic and Immunogenicity Sampling Schedule for the Atezo-G-Benda Treatment Group (cont.)

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	Serum Atezolizumab Pharmacokinetic Sample	Serum Obinutuzumab HAHA Sample	Serum Atezolizumab ATA Sample
Months 7, 15, and 23	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)
Treatment discontinuation		x	x	x	x
120 days (± 30 days) after last dose of obinutuzumab and last dose of atezolizumab (as appropriate for sample)		x	x	x	x
1 year after the last dose of obinutuzumab and last dose of atezolizumab (as appropriate for sample)		x	x	x	x

ATA = anti-therapeutic antibody; Atezo-G-benda = atezolizumab in combination with obinutuzumab plus bendamustine; FL = follicular lymphoma; HAHA = human anti-human antibody.

[a] Following analysis of the serum pharmacokinetic sample for obinutuzumab quantitation, the remaining sample may be used for HAHA analysis (if HAHA analysis is not already planned at that timepoint) at the discretion of the clinical pharmacologist and/or the clinical scientist, should there be any unusual results in the obinutuzumab concentrations.

[b] If the Cycle 1, Day 1 dose of obinutuzumab is split over 2 days, take the "30 minutes after the end of infusion obinutuzumab" PK sample relative to the end of the infusion on Day 2, and ensure that the date and time of the PK collection are accurately recorded.

Appendix 5
Pharmacokinetic and Immunogenicity Sampling Schedule for the Atezo-G-CHOP Treatment Group

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	Serum Atezolizumab Pharmacokinetic Sample	Serum Obinutuzumab HAHA Sample	Serum Atezolizumab ATA Sample
Induction (Cycle 1 to Cycle 6; 21-day cycles)					
Cycle 1	Day 1	Prior to obinutuzumab infusion (any time prior to dose); After obinutuzumab infusion [b] (30 min [± 10 min] after end of infusion)	—	Prior to obinutuzumab infusion (any time prior to dose)	—
Cycle 2	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose); After atezolizumab infusion (30 min [± 10 min] after end of infusion)	—	Prior to atezolizumab infusion (any time prior to dose)
Cycle 3	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)
Cycle 5	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	Prior to obinutuzumab infusion (any time prior to dose)	Prior to atezolizumab infusion (any time prior to dose)
End of Induction (Cycle 6)		Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	Prior to obinutuzumab infusion (any time prior to dose)	Prior to atezolizumab infusion (any time prior to dose)

ATA = anti-therapeutic antibody; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HAHA = human anti-human antibody.

[a] Following analysis of the serum pharmacokinetic sample for obinutuzumab quantitation, the remaining sample may be used for HAHA analysis (if HAHA analysis is not already planned at that timepoint) at the discretion of the clinical pharmacologist and/or the clinical scientist, should there be any unusual results in the obinutuzumab concentrations.

[b] If the Cycle 1, Day 1 dose of obinutuzumab is split over 2 days, take the "30 minutes after the end of infusion obinutuzumab" PK sample relative to the end of the infusion on Day 2, and ensure that the date and time of the PK collection are accurately recorded.

Appendix 5
Pharmacokinetic and Immunogenicity Sampling Schedule for the Atezo-G-CHOP Treatment Group (cont.)

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	Serum Atezolizumab Pharmacokinetic Sample	Serum Obinutuzumab HAHA Sample	Serum Atezolizumab ATA Sample
Maintenance: Patients with FL (enrolled in safety run-in phase) (Month 1 to Month 24)					
Month 1	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	Prior to obinutuzumab infusion (any time prior to dose)	Prior to atezolizumab infusion (any time prior to dose)
Month 2	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose); After atezolizumab infusion (30 min [± 10 min] after end of infusion)	—	Prior to atezolizumab infusion (any time prior to dose)
Month 3	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	—
Month 4	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)
Months 7, 15, and 23	Day 1	Prior to obinutuzumab infusion (within 5 hr prior to dose); After obinutuzumab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)
Treatment discontinuation		x	x	x	x

Appendix 5
Pharmacokinetic and Immunogenicity Sampling Schedule for the Atezo-G-CHOP Treatment Group (cont.)

Study Visit	Serum Obinutuzumab Pharmacokinetic Sample [a]	Serum Atezolizumab Pharmacokinetic Sample	Serum Obinutuzumab HAHA Sample	Serum Atezolizumab ATA Sample
Maintenance: Patients with FL (enrolled in safety run-in phase) (Month 1 to Month 24)				
120 days (±30 days) after last dose of obinutuzumab and last dose of atezolizumab (as appropriate for sample)	x	x	x	x
1 year after the last dose of obinutuzumab and last dose of atezolizumab (as appropriate for sample)	x	x	x	x

ATA=anti-therapeutic antibody; Atezo-G-CHOP=atezolizumab in combination with obinutuzumab plus CHOP; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; HAHA=human anti-human antibody.

[a] Following analysis of the serum pharmacokinetic sample for obinutuzumab quantitation, the remaining sample may be used for HAHA analysis (if HAHA analysis is not already planned at that timepoint) at the discretion of the clinical pharmacologist and/or the clinical scientist, should there be any unusual results in the obinutuzumab concentrations.

[b] If the Cycle 1, Day 1 dose of obinutuzumab is split over 2 days, take the "30 minutes after the end of infusion obinutuzumab" PK sample relative to the end of the infusion on Day 2, and ensure that the date and time of the PK collection are accurately recorded.

Appendix 6
Pharmacokinetic and Immunogenicity Sampling Schedule for with Atezo-R-CHOP Treatment Group

Study Visit		Serum Rituximab Pharmacokinetic Sample [a]	Serum Atezolizumab Pharmacokinetic Sample	Serum Rituximab HACA Sample	Serum Atezolizumab ATA Sample
Induction: Cycle 1 to Cycle 8; 21-day cycles					
Cycle 1	Day 1	Prior to rituximab infusion (any time prior to dose); After rituximab infusion (30 min [± 10 min] after end of infusion) [b]	—	Prior to rituximab infusion (any time prior to dose)	—
Cycle 2	Day 1	Prior to rituximab infusion (within 5 hr prior to dose); After rituximab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose); After atezolizumab infusion (30 min [± 10 min] after end of infusion)	—	Prior to atezolizumab infusion (any time prior to dose)
Cycle 3	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)
Cycle 5	Day 1	Prior to rituximab infusion (within 5 hr prior to dose); After rituximab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	Prior to rituximab infusion (any time prior to dose)	Prior to atezolizumab infusion (any time prior to dose)
End of induction (Cycle 8)		Prior to rituximab infusion (within 5 hr prior to dose); After rituximab infusion (30 min [± 10 min] after end of infusion)	Prior to atezolizumab infusion (within 5 hr prior to dose)	Prior to rituximab infusion (any time prior to dose)	Prior to atezolizumab infusion (any time prior to dose)

Appendix 6
Pharmacokinetic and Immunogenicity Sampling Schedule for the Atezo-R-CHOP Treatment Group (cont.)

Study Visit		Serum Rituximab Pharmacokinetic Sample a	Serum Atezolizumab Pharmacokinetic Sample	Serum Rituximab HACA Sample	Serum Atezolizumab ATA Sample
Consolidation: Cycle 9 to Cycle 25; 21-day cycles					
Cycle 9	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose); After atezolizumab infusion (30 min [±10 min] after end of infusion)	—	—
Cycle 10	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	—
Cycle 11	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	—
Cycle 12	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	—
Cycle 16	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)
Cycle 20	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	—
Cycle 25	Day 1	—	Prior to atezolizumab infusion (within 5 hr prior to dose)	—	Prior to atezolizumab infusion (any time prior to dose)
Treatment discontinuation		x	x	x	x
120 days (±30 days) after last dose of rituximab and last dose of atezolizumab (as appropriate for sample)		x	x	x	x

Appendix 6
Pharmacokinetic and Immunogenicity Sampling Schedule for the Atezo-R-CHOP Treatment Group (cont.)

Study Visit	Serum Rituximab Pharmacokinetic Sample a	Serum Atezolizumab Pharmacokinetic Sample	Serum Rituximab HACA Sample	Serum Atezolizumab ATA Sample
Consolidation: Cycle 9 to Cycle 25; 21-day cycles				
1 year after the last dose of rituximab and last dose of atezolizumab (as appropriate for sample)	x	x	x	x

ATA = anti-therapeutic antibody; Atezo = atezolizumab; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL = diffuse large B-cell lymphoma; HACA = human anti-chimeric antibody; R = rituximab.

[a] Following analysis of the serum pharmacokinetic sample for rituximab quantitation, the remaining sample may be used for HACA analysis (if HACA analysis is not already planned at that timepoint) at the discretion of the clinical pharmacologist and/or the clinical scientist, should there be any unusual results in the rituximab concentrations.

[b] If the Cycle 1, Day 1 dose of rituximab is split over 2 days, take the "30 minutes after the end of infusion rituximab" PK sample relative to the end of the infusion on Day 2, and ensure that the date and time of the PK collection are accurately recorded.

Appendix 7
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

In this study, only positron emission tomography and computed tomography (PET-CT)–based response criteria will be used with the following modifications:

- If the bone marrow was involved by lymphoma before treatment, the designation of a complete response (CR) requires normal bone marrow by morphology. If indeterminate by morphology, immunohistochemistry should be negative.
- The designation of PET-CT-based partial response (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

Appendix 7
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Table 3. 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* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, 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	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, 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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Appendix 7
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, 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

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

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid 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 (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured 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 (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†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 8
Summary of Criteria for Tumor Measurements

Summary of Criteria for Tumor Measurements

Criteria for tumor measurements, which are based on the modified Cheson 2007 criteria, are presented below.

Selection of Target Lesions at Baseline

Up to six of the largest dominant nodes or tumor masses (extranodal) should be selected according to all of the following:

- Lesions should be clearly measurable in at least two perpendicular dimensions.
- All nodal lesions must measure either >1.5 cm in long axis regardless of short axis measurement or >1.0 cm in short axis with a long axis of 1.1 to 1.5 cm.
- Measurable extranodal disease should be assessed in a manner similar to that used for nodal disease. All measurable extranodal lesions must be ≥ 1.0 cm in the long axis and twice the reconstruction interval of the scan. Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions
- If possible, the lesions should be from disparate regions of the body.
- Lesions should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

Selection of Non-Target Lesions

Non-target lesions will be qualitatively assessed at each subsequent timepoint. All of the sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including nodal and extranodal (any measurable lesions that were not chosen as target lesions), and assessable disease. Examples of non-target lesions include the following:

- All bone lesions, irrespective of the modality used to assess them
- Lymphangitis of the skin or lung
- Cystic lesions
- Splenomegaly and hepatomegaly
- Measurable lesions beyond the maximum number of six
- Groups of lesions that are small and numerous
- Pleural/pericardial effusions and/or ascites

Appendix 8
Summary of Criteria for Tumor Measurements (cont.)

For this study, a significant increase in existing pleural effusions, ascites, or other fluid collections will be considered sufficient evidence of progression and will not require cytological proof of malignancy. Effusions, ascites, or other fluid collections will be followed as non-target lesions as outlined below:

- **Existing effusions/ascites:** Effusions, ascites, or other fluid collections will be followed as non-target lesions. At each timepoint, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed.
- **New effusions/ascites:** Significant new effusions, ascites, or other fluid collections that are radiographically suggestive of malignancy should be recorded as new lesions.

Reporting Conventions

Unable to Evaluate Lesion Category

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

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

If a target lesion is classified as UE after baseline, the sum of the product of the diameters (SPD) of the target lesions cannot accurately be determined for that timepoint, a response of complete response (CR), partial response (PR), or stable disease (SD) cannot be assigned for that timepoint, and the response assessment will be UE unless unequivocal progression is determined on the basis of non-target or new lesions, or the evaluable target lesions.

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

Appendix 8
Summary of Criteria for Tumor Measurements (cont.)

Too Small to Measure Lesion Category

In this trial, an average threshold of detection limit is set at 5 mm. Any target lesion findings identified on baseline images that decrease in size to < 5 mm in any dimension at a subsequent timepoint should be categorized as too small to measure. The lesion, node, or mass should be assigned measurements of 5 $\times$ 5 mm (for the long axis and the short axis) on the source document for the purpose of calculating the area. If that lesion increases in size to ≥ 5 mm in any dimension afterwards, its true size (long axis and short axis) should be recorded. The purpose of the assigned value for the measurement is the acknowledgment that small findings are not accurately measured.

Appendix 8
Summary of Criteria for Tumor Measurements (cont.)

Timepoint Radiological Response

Target Lesions	Non-Target Lesions	New Lesion [a]	Timepoint Response
CR	CR	No	CR
CR	SD	No	PR
CR	UE	No	UE
PR	UE	No	UE
PR	CR	No	PR
PR	SD	No	PR
SD	UE	No	UE
SD	CR	No	SD
SD	SD	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
UE	Non-PD	No	UE
UE	UE	No	UE
CR	NA [b]	No	CR
PR	NA [b]	No	PR
SD	NA [b]	No	SD
NA [c]	SD	No	SD
NA [c]	CR	No	CR
NA [c]	UE	No	UE
NA [c]	NA [b]	No	UE

CR = complete response; NA = not applicable; PD = progressive disease; PR = partial response; SD = stable disease; UE = unable to evaluate.

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

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

[c] No target lesions identified at baseline.

Adapted from:

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

Appendix 8
Summary of Criteria for Tumor Measurements (cont.)

Response should be determined on the basis of computed tomography (CT) scan and confirmed with positron emission tomography (PET)-CT using the modified Cheson 2007 criteria. The modified Cheson 2007 criteria are presented below, with slight modifications for consistency with the protocol.

Assessment of positive PET scans should follow the criteria described by Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma (Juweid et al. 2007). A positive focal or diffuse fluorodeoxyglucose (FDG)-PET scan is defined as follows: FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff.

Complete Response

Based on CT imaging, the designation of CR requires all of the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy must be demonstrated.
- The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal in size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
- If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate ($>$20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Based on PET-CT imaging, the designation of CR requires the following:

- For patients with a positive PET scan before treatment: Post-treatment residual masses of any size must be PET negative.

Appendix 8
Summary of Criteria for Tumor Measurements (cont.)

Partial Response

Based on CT imaging, the designation of PR requires all of the following:

- A ≥ 50% decrease in the SPD of up to six of the largest dominant nodes or nodal masses must be demonstrated. These nodes or masses should be selected according to all of the following: (a) they should be clearly measurable in at least two perpendicular dimensions; (b) if possible, they should be from disparate regions of the body; and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase in the size of the other nodes, liver, or spleen should be observed.
- Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the long axis.
- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement, will be considered partial responders.
- No new sites of disease should be observed (e.g., nodes > 1.5 cm in any axis).

Based on PET-CT imaging, the designation of PR requires the following:

- For patients with a positive PET scan before treatment: The post-treatment PET should be positive in at least one previously involved site.

Stable Disease

Based on CT imaging, SD is defined as the following:

- The patient does not meet the criteria needed for a CR or PR and does not meet the criteria for progressive disease (see below).

Based on PET-CT imaging, SD is defined as the following:

- For patients with a positive PET scan before treatment: The PET scan should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET-CT scan.

Appendix 8
Summary of Criteria for Tumor Measurements (cont.)

Progressive Disease

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

Based on CT imaging, the designation of progressive disease (PD) requires any of the following:

- Appearance of any new lesion >1.5 cm in any axis during or at the end of therapy is demonstrated, even if other lesions are decreasing in size.
- There is a $\geq 50\%$ increase from the nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of <1.0 cm must increase by $\geq 50\%$ and to a size of 1.5×1.5 cm, or >1.5 cm in the long axis.
- There is a $\geq 50\%$ increase in the long axis of any single previously identified node with a short axis >1 cm.

Based on PET-CT imaging, the designation of PD requires any of the following:

- For patients with a positive PET scan before treatment: Lesions should be PET positive, unless the lesion is too small to be detected with current PET system (<1.5 cm in its long axis by CT).

  Increased FDG uptake in a previously unaffected site should only be considered progressive disease after confirmation with other modalities.

Additional Response Assessment Guidelines

If a small increase is seen in only one lesion, a new evaluation after some weeks may be necessary to determine whether there was true progression in that lesion.

Because the potential for tumor flares with immunotherapies increases the risk of false positive PET-CT scans in lymphoma, caution must be exercised to avoid confusing the possible tumor flare with progressive disease. In the event of residual metabolically active tissue, it is recommended that either a biopsy be performed or the lesion be reassessed in at least 2 weeks; if there is continued evidence of tumor progression, the date of progressive disease should be the date of the previous evaluation.

Appendix 8
Summary of Criteria for Tumor Measurements (cont.)

REFERENCES

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

Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the imaging subcommittee of international harmonization project in lymphoma. J Clin Oncol 2007;25:571–8.

Appendix 9
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 10
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 11
Follicular Lymphoma International Prognostic Index and 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.

Appendix 11
Follicular Lymphoma International Prognostic Index and International Prognostic Index (cont.)

Table 2 Follicular Lymphoma International Prognostic Index 2

FLIPI2 Risk Factor
Bone marrow involvement
Age >60 years
$\beta 2$ 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 11
Follicular Lymphoma International Prognostic Index and International Prognostic Index (cont.)

Table 3 International Prognostic Index

IPI Risk Factor	
Ann Arbor Stage III or IV	
Age >60 years	
Serum LDH $>1\times$ ULN	
ECOG Performance Status ≥ 2	
Extranodal involvement ≥ 2	
IPI Risk Group	**Number of IPI Risk Factors**
Low	0 or 1
Low – Intermediate	2
High – Intermediate	3
High	4 or 5

ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; IPI = 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 IPI since this prognostic score was established without FDG-PET.

Adapted from:

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

Appendix 12
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 13
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 13
Preexisting Autoimmune Diseases (cont.)

COMMONLY USED CYP1A2 INHIBITORS AND INDUCERS

Based on the product information for bendamustine, no formal clinical assessments of pharmacokinetic drug–drug interactions between bendamustine and other drugs have been conducted. Bendamustine's active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl-bendamustine (M4), are formed via cytochrome P450 (CYP)1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites. The medications listed below are not contraindicated; however, caution should be used, or alternative treatments with medications that are not CYP1A2 inhibitors or inducers should be considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed for the patient's medical condition. This list is not exhaustive (adapted from ctep.cancer.gov/protocolDevelopment/docs/cyp1a2.doc).

CYP1A2 Inhibitors	CYP1A2 Inhibitors (continued)
Amiodarone	Ketoconazole
Amitriptyline	Lidocaine
Amlodipine	Losartan
Anastrozole	Erythromycin
Caffeine	Estrogens
Cimetidine	Mexiletine
Ciprofloxacin	Modafenil
Citalopram nifedipine	Olanzapine
Clarithromycin	Omeprazole
Clotrimazole	Ondansetron
Clozapine	Paroxetinee
Diclofenac	Propafenone
Diltiazem	Propanolol
Echinacea	Ranitidine
Ethinyl estradiol	Sertraline
Fluoroquinolones	
Fluconazole	
Fluvoxamine	
Gemfibrozil	
Ginseng	
Imipramine	
Isoniazid	

Appendix 13
Preexisting Autoimmune Diseases (cont.)

CYP1A2 Inducers
Barbiturates (e.g., phenobarbital)
Cruciferous vegetables (broccoli, cauliflower, arugula, brussel sprouts, cabbage, kale, chard, turnips, radishes, wasabi, bok choy, watercress, collard greens)
Char-grilled meat
Carbamazepine
Primidone
Rifampin
Smoking
Triamterene
Zolmitriptan

Below is a sample card to be handed to patients in the BO29563 study. This card may be adapted to comply with local guidelines.

During this clinical study, I am receiving a drug called bendamustine. This drug is approved for the treatment of lymphoma in the United States of America and a number of the European Union member states. The following medications and substances are examples of drugs and substances that may alter blood levels of bendamustine:

Fluvoxamine

Ciprofloxacin

Omeprazole

Smoking

Caution must be used or alternative treatments be considered if treatment with one of these listed drugs or substances or another CYP1A2 inhibitor or inducer is needed. If you have further questions, please contact the study doctor whose name and contact number are indicated on the other side of this card.

Appendix 14
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.