Official Title: **A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF ATEZOLIZUMAB IN COMBINATION WITH OBINUTUZUMAB PLUS LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA**

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PROTOCOL

TITLE: **A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF ATEZOLIZUMAB IN COMBINATION WITH OBINUTUZUMAB PLUS LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA**

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TEST PRODUCTS: Obinutuzumab (RO5072759)
Atezolizumab (RO5541267)

MEDICAL MONITOR: [redacted], Ph.D.

SPONSOR: F. Hoffmann-La Roche Ltd

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Version 7: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	07-Nov-2018 02:06:38

CONFIDENTIAL

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PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol BO29562 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 5.1.2 and 5.1.5.2 [Table 12]).
- Considering no new safety signals have been identified with atezolizumab in combination with obinutuzumab plus lenalidomide, once all patients have completed/discontinued maintenance, regular Internal Monitoring Committee assessments will no longer take place and ad hoc meetings maybe called at the discretion of the Medical Monitor in case of newly identified safety signals (Section 3.1.4).
- Post-trial access language was changed allowing patients still under study treatment to enter an extension study in case of earlier closure of Study BO29562 (Section 4.3.4).
- The Medical Monitor information has been updated (Section 5.4.1).
- The Lenalidomide Summary of Product Characteristics has replaced local labels as the reference document for determining reporting requirements for single adverse events (Section 5.7).

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 APMAMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF ATEZOLIZUMAB IN COMBINATION WITH OBINUTUZUMAB PLUS LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA**
PROTOCOL NUMBER:	BO29562
VERSION NUMBER:	7
EUDRACT NUMBER:	2015-002467-42
IND NUMBER:	122,847
TEST PRODUCTS:	Obinutuzumab (RO5072759) Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF ATEZOLIZUMAB IN COMBINATION WITH OBINUTUZUMAB PLUS LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA**
PROTOCOL NUMBER:	BO29562
VERSION NUMBER:	7
EUDRACT NUMBER:	2015-002467-42
IND NUMBER:	122,847
TEST PRODUCTS:	Obinutuzumab (RO5072759) Atezolizumab (RO5541267)
PHASE:	Phase Ib/II
INDICATION:	Follicular or diffuse large B-cell lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Outcome Measures

This study will evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of induction treatment consisting of atezolizumab in combination with obinutuzumab plus lenalidomide (Atezo + G + Len) in patients with relapsed or refractory follicular lymphoma (FL), followed by maintenance treatment with Atezo + G + Len in patients who achieve a complete response (CR), a partial response (PR), or stable disease at end of induction (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 Objectives

The safety objectives for this study are as follows:

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

  Incidence of dose-limiting toxicities during Cycle 2 of study treatment

- To evaluate the safety and tolerability of Atezo + G + Len 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-computed tomography (PET-CT) scans or CT scans alone, using Revised Lugano Response Criteria for Malignant Lymphoma, hereinafter referred to as Lugano 2014 criteria. 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 Atezo + G + Len on the basis of the following endpoint:

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

Secondary Efficacy Objectives

The secondary efficacy objective for this study is to evaluate the efficacy of induction and maintenance treatments with Atezo + G + Len on the basis of the following endpoints:

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

Exploratory Efficacy Objectives

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of Atezo + G + Len 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 on the basis of PET-CT scans
- Progression-free survival (PFS), defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by the investigator on the basis of CT scans alone or death from any cause
- Event-free survival (EFS), defined as the time from initiation of study treatment to any treatment failure, including disease progression or relapse, as determined by the investigator on the basis of CT scans alone; initiation of new anti-lymphoma therapy; or death from any cause, whichever occurs first
- Disease-free survival (DFS), defined as the time from the first occurrence of a documented CR to relapse among patients achieving a CR, as determined by the investigator on the basis of CT scans alone or death from any cause, whichever occurs first
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to the time of disease progression or relapse, as determined by the investigator on the basis of CT scans alone or death from any cause, whichever occurs first.
- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of atezolizumab, obinutuzumab, and lenalidomide, when given in combination, on the basis of the following endpoints:

- Observed serum obinutuzumab concentration at specified timepoints
- Observed serum atezolizumab concentration at specified timepoints
- Observed plasma lenalidomide concentration at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab 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 anti-therapeutic antibodies to atezolizumab during the study relative to the prevalence of anti-therapeutic antibodies at baseline

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

- Correlation between HAHA or anti-therapeutic antibody status and efficacy, safety, or PK endpoints

Biomarker Objective

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

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

Study Design

Description of Study

This Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study will evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of Atezo + G + Len in patients with relapsed or refractory FL. The study will include an initial dose-escalation phase designed to determine the RP2D for lenalidomide in this treatment combination followed by an expansion phase in which lenalidomide will be given at the RP2D. All patients will receive induction treatment with Atezo + G + Len for six cycles. Patients achieving a CR, a PR, or stable disease at EOI will be eligible to receive extended dosing of Atezo + G + Len as maintenance treatment (refer to protocol for details on treatment regimens). A study schema is provided in the protocol.

Overall, it is planned to have approximately 46 patients enrolled in this study at approximately 15 investigative sites around the world, mainly in Europe and North America.

All patients will be closely monitored for adverse events throughout the study and for at least 35 days after the last dose of study treatment. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0. An Internal Monitoring Committee (IMC) will be established to monitor patient safety throughout the study.

To characterize the PK properties of obinutuzumab, atezolizumab, and lenalidomide as well as the immunogenicity of obinutuzumab and atezolizumab when given in combination, blood samples will be taken at various timepoints before and during dosing.

Response will be determined by the IRC and the investigator using the Lugano 2014 criteria. The primary efficacy endpoint will be based on IRC assessment of response. Refer to protocol for details on tumor assessments.

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

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

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

Number of Patients

Overall, it is planned to have approximately 46 patients enrolled in this study at approximately 15 investigative sites around the world, mainly in Europe and North America.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- ECOG Performance Status of 0, 1, or 2
- Relapsed or refractory FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator
- Histologically documented CD20-positive lymphoma as determined by the local laboratory
- 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

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

  If the available biopsy was performed more than 12 months prior to Day 1 of Cycle 1 for patients with FL, or the patient received anti-lymphoma treatment between the time of the most recent available biopsy and Day 1 of Cycle 1, a core-needle biopsy is strongly recommended.
- Agreement to comply with all local requirements of the lenalidomide risk minimization plan

  In every country where lenalidomide has been approved, a risk minimization plan, which includes a pregnancy prevention program, is in place. The risk minimization plan should be followed by patients using lenalidomide. In addition, because lenalidomide will be administered in combination with atezolizumab and obinutuzumab, patients must comply with contraceptive measures designed to ensure safe administration of all three study treatments, as outlined below.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, for at least 28 days prior to Day 1 of Cycle 1, during the treatment period (including periods of treatment interruption), and for at least 18 months after the last dose of study treatment

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

Examples of non-hormonal contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established and proper use of progestogen-only hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Combined oral contraceptives are not recommended because of the increased risk of venous and arterial thromboembolism (TE) in patients taking lenalidomide.

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

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 or 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 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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:

- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Known CD20-negative status at relapse or progression
- CNS lymphoma or leptomeningeal infiltration
- Prior allogeneic stem-cell transplant (SCT)
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1
- History of resistance to lenalidomide or response duration of <1 year (for patients who had a response to a prior lenalidomide-containing regimen)
- Prior standard or investigational anti-cancer therapy as specified below:

  Lenalidomide, fludarabine, or alemtuzumab within 12 months prior to Day 1 of Cycle 1

  Radioimmunoconjugate within 12 weeks prior to Day 1 of Cycle 1

  Monoclonal antibody or 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

  Anti–PD-1, anti–PD-L1, anti-CTLA4, anti–CD137/41-BB agonist, or anti-CD40 agonist antibodies
- Clinically significant toxicity (other than alopecia) from prior treatment that has not resolved to Grade ≤ 2 (per NCI CTCAE v4.0) prior to Day 1 of Cycle 1

- Treatment with systemic immunosuppressive medications, including, but not limited to, prednisone, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor agents within 2 weeks prior to Day 1 of Cycle 1

  Treatment with inhaled corticosteroids and mineralocorticoids is permitted.

  If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, 100 mg of prednisone or equivalent can be given for a maximum of 5 days, but all tumor assessments must be completed prior to initiation of corticosteroid treatment.
- History of solid organ transplantation
- History of severe allergic or anaphylactic reaction to humanized, chimeric or murine monoclonal antibodies
- Known sensitivity or allergy to murine products
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab, obinutuzumab, or lenalidomide formulation, including mannitol
- History of erythema multiforme, Grade ≥ 3 rash, or blistering following prior treatment with immunomodulatory derivatives such as thalidomide and lenalidomide
- 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 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 progressive multifocal leukoencephalopathy
- 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:

  Any of the following malignancies previously 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, low-grade, early-stage localized prostate cancer, or any other previously treated malignancy that has been in remission without treatment for ≥ 5 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.
- Contraindication to treatment for TE prophylaxis

- Grade $\geq$ 2 neuropathy
- 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
- 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):

  Calculated creatinine clearance $<$ 60 mL/min

  AST or ALT $>$ 2.5 times the upper limit of normal (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 of childbearing potential must have two negative serum pregnancy test results (minimum sensitivity, 25 mIU/mL) prior to initiating therapy: at 10–14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1.
- Life expectancy $<$ 3 months
- Unable to comply with the study protocol, in the investigator's judgment

End of Study

The end of this study is defined as the time when all enrolled patients have completed or discontinued study treatment (including induction treatment and maintenance treatment as applicable).

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 by intravenous 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. No dose modification for obinutuzumab is allowed.

Atezolizumab will be administered at a flat dose consisting of one of the following: 1) 840 mg every 2 weeks (840 mg on Days 1 and 15 of Cycles 2–6, given in 28-day cycles as induction treatment) and 2) 1680 mg every 4 weeks (840 mg on Days 1 and 2 of each month, given as maintenance treatment). No dose modification for atezolizumab is allowed.

Lenalidomide will be administered orally once daily on Days 1–21 of Cycles 1–6 (28-day cycles) during induction treatment and on Days 1–21 of each month during maintenance treatment. During the dose-escalation phase, lenalidomide will be administered at a dose of 15 or 20 mg (dose may be de-escalated to 10 mg) during induction treatment and at 10 mg during maintenance treatment. During the expansion phase, lenalidomide will be administered at the RP2D during induction treatment and at 10 mg during maintenance treatment.

Statistical Methods

Primary Analysis

Safety

The safety analysis will be performed on the primary population; additional safety analysis will be performed on the intent-to-treat (ITT) population.

The safety analyses will be performed separately for each study phase (i.e., dose escalation and expansion).

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 the first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 grade. All serious adverse events, adverse events of special interest, and selected events 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 data will be displayed by time, with Grade 3 and 4 values identified as appropriate.

Efficacy

The efficacy analysis will be performed on the primary population. Additional efficacy analysis will be performed on the ITT population.

Patients who received lenalidomide at the RP2D during the dose-escalation phase will be pooled with patients treated in the expansion phase.

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. Patients without an EOI tumor assessment will be considered non-responders.

Determination of Sample Size

Limited dose finding will be conducted during the dose-escalation phase of this study. The estimated sample size follows from the dose-escalation rules for a 3+3 algorithm, as outlined in the protocol. It is anticipated that enrollment of two dosing groups of 3–6 patients each, for a total of 6–12 patients with relapsed or refractory FL, will be required to establish the RP2D during the dose-escalation phase.

Approximately 40 patients will be enrolled during the expansion phase.

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 from the GALEN study (Morschhauser et al. 2017) indicate that the historical CR rate based on PET-CT scans is approximately 40% in relapsed or refractory setting, 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 $<46\%$, assuming an observed PET-CT–defined CR rate of 60%. Updated estimates of the proportion of patients expected to achieve a PET-CT–defined CR 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 treated at the RP2D of lenalidomide have been evaluated for PET-CT–defined CR at the EOI. Additional analyses will be conducted approximately every 4 months to guide early stopping of enrollment for safety on the basis of observed toxicities. Stopping rules for excess toxicity, including fatal adverse events, have been included.

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 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 is lower or higher than expected, the IMC will review the data and decide whether to recommend an early decision to stop enrollment. 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALP	alkaline phosphatase
ATA	anti-therapeutic antibody
Atezo	atezolizumab
AUC	area under the concentration–time curve
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CLL	chronic lymphocytic leukemia
CR	complete response
CT	computed tomography
C_{trough}	trough concentration
CYP	cytochrome P450
DDI	drug–drug interaction
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of objective response
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
EOM	end of maintenance
EORTC	European Organization for Research and Treatment of Cancer
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FL	follicular lymphoma
FLIPI, FLIPI2	Follicular Lymphoma International Prognostic Index Follicular Lymphoma International Prognostic Index 2
G	obinutuzumab (GA101)
GB	obinutuzumab plus bendamustine
GCP	Good Clinical Practice
G-CHOP	obinutuzumab plus CHOP
G-CSF	granulocyte colony-stimulating factor
GEP	gene expression profile

Abbreviation	Definition
GI	gastrointestinal
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-γ	interferon gamma
IL	interleukin
IL-2	interleukin-2
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
ITT	intent to treat
IV	intravenous
IxRS	interactive voice or web-based response system
JC	John Cunningham
Len	lenalidomide
LFT	liver function test
LMWH	low-molecular-weight heparin
Lugano 2014 criteria	Lugano Response Criteria for Malignant Lymphoma
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NK	natural killer
NSCLC	non–small cell lung cancer

Abbreviation	Definition
ORR	overall response rate
OS	overall survival
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
R-CHOP	rituximab plus CHOP
RANKL	receptor activator of nuclear factor kappa-B ligand
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RP2D	recommended Phase II dose
SCT	stem-cell transplantation
SPM	second primary malignancy
T4	thyroxine
TE	thromboembolism
Teff	T cell
TFH	follicular helper T cell
TFR	tumor flare reaction
TIL	tumor-infiltrating lymphocyte
TLS	tumor lysis syndrome
TSH	thyroid-stimulating hormone
UC	urothelial carcinoma
ULN	upper limit of normal
UBC	urothelial bladder cancer

1. BACKGROUND

1.1 BACKGROUND ON FOLLICULAR LYMPHOMA

Indolent non-Hodgkin lymphoma (iNHL) refers to a heterogeneous group of malignant B-cell lymphomas and account for approximately one-third of all non–Hodgkin's lymphomas (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 with the IgH locus and results in the overexpression of the anti-apoptotic protein, Bcl-2.

Despite currently available therapies, FL remains an incurable disease. The addition of rituximab, an anti-CD20 monoclonal antibody, to commonly used induction chemotherapy (including cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]; cyclophosphamide, vincristine, and prednisone; fludarabine; or bendamustine [Dreyling et al. 2014; Zelenetz et al. 2014]) followed by rituximab maintenance therapy, leads to prolonged remission and improved patient outcomes. Updated results from Study MO18264 confirmed the benefit of 2-year rituximab maintenance in patients responding to first-line immunotherapy, with a 6-year progression-free survival (PFS) of 59.2% compared with 42.7% in the observation arm (hazard ratio [HR] $= 0.625$; $p < 0.0001$; 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 by decreasing duration of response to subsequent lines of therapy. Thus, new treatments are needed to improve the outcome for these patients. Several Phase II studies documented the high potential of the rituximab plus lenalidomide combination, which was first tested in relapsed FL (Tuscano et al. 2014; Leonard et al. 2012) and, more recently, as initial treatment for FL (Fowler et al. 2014; Martin et al. 2014). The overall response rate (ORR) in previously untreated patients with FL was 98%, with 87% of the patients achieving complete and durable responses and 90% of patients becoming positron emission tomography (PET)-computed tomography (CT) negative and achieving a molecular remission (Fowler et al. 2014). Based on these data, this regimen is currently being investigated in a randomized Phase III study in previously untreated patients with FL (RELEVANCE; ClinicalTrial.gov, number NCT01476787).

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 FcγRIII receptors expressed on natural killer (NK) cells, macrophages, and monocytes, resulting in enhanced antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis (Beers et al. 2010; Mössner et al. 2010; Herter et al. 2014). Together, these

characteristics confer obinutuzumab with enhanced immune effector functions and B-cell-depleting activity compared with rituximab.

Obinutuzumab is approved for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). Obinutuzumab is also approved for use in combination with bendamustine followed by obinutuzumab maintenance for the treatment of patients with FL who did not respond to or who progressed during or after treatment with rituximab or a rituximab-containing regimen.

1.2.1 Nonclinical Studies with Obinutuzumab

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

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

1.2.2 Clinical Studies with Obinutuzumab

To date, clinical data from studies sponsored by F. Hoffmann-La Roche Ltd. (the Sponsor) on obinutuzumab are available from eight Phase I or II studies (Studies BO20999, BO21003, JO21900, BO21000, GAO4915g, GAO4779g, YP25623, and GAO4768g) and five Phase III studies (GAO4753g, BO21004/CLL11, MO28543, BO21223, and BO21005). The available efficacy results from the NHL cohorts in these studies and available safety and pharmacokinetic (PK) results from all patients are summarized in Sections 1.2.2.1 and 1.2.2.3.

For more detailed clinical information on obinutuzumab, including results in the CLL cohorts of the clinical studies and exposure data, 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, YP25623, and JO21900), the proportion of patients who had a response (complete response [CR] or partial response [PR]) at the end of treatment (as determined on the basis of 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 and bendamustine) in patients with previously untreated or relapsed or refractory NHL (Studies BO21000, GAO4915g, and GAO4753g), the proportion of patients with a CR or PR at the end of induction (EOI) treatment ranged from 69% to 96%. The CR rate was higher with combination therapy (35%–39% in patients with previously untreated FL, 39%–50% in patients with relapsed or refractory FL, and 55% in patients with previously untreated diffuse large B-cell lymphoma [DLBCL]) than with monotherapy.

A Phase III study, Study BO21223, investigated obinutuzumab (G)+chemotherapy (obinutuzumab plus bendamustine and obinutuzumab plus CHOP [G-CHOP]) compared with rituximab+chemotherapy in patients with previously untreated iNHL (FL cohort, n=1202). On the basis of positive results from a pre-planned interim analysis of this study, demonstrating significant improvement in PFS in the G-chemotherapy arm, the Independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor.

A Phase III study, Study BO21005, investigated G-CHOP compared with rituximab+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 30 April 2016, an estimated 4454 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 vs. 2000 mg), the incidence of deaths did not increase with increased obinutuzumab dose (7.5% vs. 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 patients with previously untreated CLL who received obinutuzumab plus chlorambucil (Study BO21004) to 100% in patients with relapsed or refractory CLL who received obinutuzumab monotherapy (pooled data from the CLL cohorts in Studies BO21003 and BO20999). Anaphylaxis has also been reported in patients treated with obinutuzumab.

In the NHL population, the incidence of IRRs in studies of obinutuzumab monotherapy was 75.1% (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, regardless the relationship with obinutuzumab, was 70%–78%.

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 and hepatitis B virus [HBV] reactivation), worsening of preexisting cardiac conditions, gastrointestinal (GI) perforation, impaired immunization response immunogenicity, and second malignancies. The important identified risks associated with obinutuzumab are presented in detail in Section 5.1.1 and in the Obinutuzumab Investigator's Brochure.

1.2.2.3 Clinical Pharmacokinetics of Obinutuzumab

On the basis of available PK data, a two-compartment PK model comprising both a linear clearance pathway and a non-linear time varying clearance pathway adequately described serum obinutuzumab concentration data. The initial clearance of obinutuzumab was approximately 2.8 times higher than the steady-state clearance, consistent with a decrease in the time-varying clearance component, which was high at the start of treatment and declined with repeated cycles of obinutuzumab treatment. The time-varying clearance pathway is consistent with target-mediated drug disposition, such that at the start of treatment, when there is a large quantity of CD20-positive cells, this rapidly binds obinutuzumab. Repeated dosing of obinutuzumab saturates the pool of CD20-positive cells, hence reducing this component in clearance. The linear clearance pathway is consistent with catabolism of Ig G antibodies and is therefore independent of CD20-positive cells. Refer to the Obinutuzumab Investigator's Brochure for additional details.

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 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 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's duration. Enhanced combination efficacy was also observed in a study using A20 cells transfected with human CD20 and green fluorescent protein (data available on request).

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

1.3.2 Clinical Studies with Atezolizumab

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies. The majority of the safety and efficacy data summarized below are from Phase Ia study PCD4989g, a multicenter, first-in-human, open-label, dose-escalation trial evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, 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., FOLFOX [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 50.2% of patients.

Treatment-related adverse events (per investigator's assessment of causality) were reported in 444 of 629 (70.6%) patients. Related Grade 3–4 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 (≥ 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% 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%), 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 5.1.5.

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

1.3.2.2 Clinical Pharmacokinetics of Atezolizumab

On the basis of available preliminary PK data (0.03 – 20 mg/kg), atezolizumab showed linear pharmacokinetics at doses ≥ 1 mg/kg. Serum atezolizumab concentrations exhibited a biphasic disposition with an initial rapid distribution phase followed by a slow elimination phase. For the 1- and 20-mg/kg dose groups, the mean apparent clearance and the mean volume of distribution at steady state had a range of 3.50–3.55 mL/day/kg and 48.1 to 65.7 mL/kg, respectively, which is consistent with the expected PK profile of an IgG1 antibody in humans. Atezolizumab exhibited non-linear pharmacokinetics at doses of < 1 mg/kg (i.e., 0.03−0.3 mg/kg), which is likely due to target-mediated clearance at lower concentrations. Refer to the Atezolizumab Investigator's Brochure for additional details.

1.3.2.3 Summary of Clinical Activity of Atezolizumab

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

Efficacy results, based on a data cutoff 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 additional details.

Patients with Non–Small Cell Lung Cancer

Objective responses were reported in 20 of 88 (22.7%) efficacy-evaluable patients with locally advanced or metastatic NSCLC; responses were seen in squamous and non-squamous histologies (4 of 21 and 16 of 67, respectively). Higher response rates were associated with higher PD-L1 expression (50.0% in TC3 or IC3 versus 33.3% in TC2/3 or IC2/3 versus 22.7% in all patients).

Patients with Urothelial Bladder Cancer

Objective responses were reported in 24 of 94 (25.5%) efficacy-evaluable patients with locally advanced or metastatic UBC. Responses were observed in all PD-L1 subgroups, with higher response rates associated with higher PD-L1 expression in ICs (ORRs ranged from 20.8% in patients with IC0/1 to 31.8% in patients with IC2/3). Median PFS and 1-year PFS also appeared to be associated with PD-L1 IC status.

Patients with Renal Cell Carcinoma

Objective responses were reported in 10 of 65 (15.4%) efficacy-evaluable patients with clear cell RCC. Higher response rates were associated with higher PD-L1 expression, ranging from 9.1% in IC0 patients to 19.4% in patients with IC1, IC2, or IC3. Duration of response also varied by IC score. The small sample size limits further interpretation.

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.

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 remains an area of high medical need (see Section 1.1). Patients ultimately relapse, and subsequent active and well-tolerated therapies are needed. Emerging evidence of the activity of new drugs that target the cell surface (e.g., monoclonal antibodies), microenvironment (immunomodulatory drugs such as lenalidomide), and checkpoint inhibitors that target the PD-1/PD-L1 axis opens the way to chemotherapy-free approaches as a new treatment paradigm. This study will evaluate the activity of a novel triplet combination of obinutuzumab, atezolizumab, and lenalidomide.

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 2005). 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. 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

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

Pidilizumab (CT-011), a humanized IgG-1κ monoclonal antibody that targets PD-1, has been tested in Phase I and II clinical trials in hematologic malignancies. Pidilizumab administered as a single agent after autologous stem cell transplantation (SCT) in patients with DLBCL (Armand et al. 2013) or in combination with rituximab in patients with relapsed FL (Westin et al. 2014) was well tolerated and showed potential clinical benefit. No autoimmune- or treatment-related Grade 3 or 4 adverse events have been reported in these studies. Among patients with relapsed FL who received pidilizumab in combination with rituximab (n=32), responders have been shown to express higher levels of PD-L1 on peripheral blood T cells and monocytes at baseline relative to non-responders. Additionally, in this study, gene expression profile (GEP) analysis performed on baseline tumor biopsy specimens from 18 patients showed a correlation between PFS and gene expression signature of activated T cells. GEP studies identified 41 genes more highly expressed in Teffs compared with follicular helper T cells (TFHs). Low expression of this signature suggests a higher number of TFHs and lower number of Teffs within the tumor. Consistent with the expectation that Teffs are likely to have anti-tumor effects, whereas TFHs are likely to have pro-tumor effects, a low expression of this signature is predictive of less tumor shrinkage and resulted in a shorter PFS in this study. Median PFS was 12.7 months (95% CI: 6.5, 21.6) for patients with low signature expression; median PFS was not reached for patients with high signature expression (Westin et al. 2014).

Nivolumab (BMS-936558), a fully human IgG4 monoclonal antibody that targets PD-1, was recently evaluated in a Phase I dose-escalation study that tested doses of 1 and 3 mg/kg in patients with relapsed or refractory lymphoid malignancies. Preliminary data indicate that 1 patient experienced 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 is in progress at this dose; Lesokhin et al. 2014). The 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, a first-in-class PD-L1 inhibitor being tested in multiple tumor types (which will be included in the regimen administered in the current study), has also shown activity in lymphoma (see Section 1.3.2 for a summary of results).

1.4.3 Rationale for Treatment Combination

1.4.3.1 Nonclinical Data

Obinutuzumab and Atezolizumab

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

Obinutuzumab and atezolizumab have complementary mechanisms of action, acting at different steps of the anti-tumor immune response. Obinutuzumab induces 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/B (CD16a/b). Thus, obinutuzumab has the ability to enhance T-cell priming and immune-cell activation through interactions with NK cells, T cells, monocytes/macrophages, dendritic cells, and neutrophils cells carrying FcγRIIIA or FcγRIIIB. Atezolizumab affects primarily the effector phase of the immune response by restoring cytotoxic T-cell function.

Studies of obinutuzumab plus atezolizumab have not been performed in nonclinical murine models because there are no suitable models for testing the combination. However, synergism was exhibited when the combination of a surrogate anti-mouse PD-L1 antibody, and an anti-mouse CD20-depleting antibody was tested using a syngeneic A20 lymphoma model in immune-competent mice (see Section 1.3.1). Although the anti-CD20 agent used in this study is not completely identical to obinutuzumab, the results provide compelling proof of concept for exploring this combination in clinical trials.

Lenalidomide

Lenalidomide, a thalidomide analogue, is a potent immunomodulatory agent with activity in lymphoid malignancies occurring primarily through immune modulation and direct anti-tumor effects. Currently, lenalidomide is approved for the treatment of multiple myeloma, deletion 5q myelodysplastic syndromes, and mantle cell lymphoma.

Nonclinical studies demonstrated that T-cell immune synapse dysfunction in FL can be restored with lenalidomide (Ramsay et al. 2009). In addition, lenalidomide has been shown to reduce T regulatory cells and activate CD8 T cells (Kater et al. 2014). E3 ligase protein cereblon (encoded by the CRBN gene) is the molecular target of lenalidomide. Lenalidomide binding to CRBN mediated its direct anti-tumor effects and is also required for T-cell production of interleukin-2 (IL-2) and tumor necrosis factor α (Lopez-Girona et al. 2012).

In nonclinical studies, lenalidomide combined with rituximab resulted in anti-tumor effects via increased NK cell function, enhanced antibody-dependent cell-mediated cytotoxicity, and improved NK cell–mediated synapse formation (Wu et al. 2008; Zhang et al. 2009).

The combination of obinutuzumab with lenalidomide has been evaluated in nonclinical studies using the mantle cell lymphoma Z138 xenograft model in severe combined immunodeficient-beige mice. Results from these studies demonstrated greater anti-tumor efficacy than either drug as a single agent and superior activity to the combination of lenalidomide with rituximab (data available on request [RDR 1064289]).

1.4.3.2 Available Clinical Data

BO29562 is the only study currently evaluating the combination of atezolizumab, obinutuzumab, and lenalidomide in lymphoma.

A Phase Ib study of atezolizumab in combination with obinutuzumab in patients with relapsed or refractory FL and DLBCL (Study GO29383) is currently in progress, sponsored by Roche. Preliminary results indicated that atezolizumab combined with obinutuzumab is well tolerated with evidence of clinical activity in this patient population (Palomba et al. 2016). A total of 49 patients were enrolled and dosed: 26 with FL and 23 with DLBCL. The doublet combination appears to be safe and tolerable, and is consistent with what has been observed with the respective single agents and the diseases under study. As of the 14 June 2017 data cutoff, a review of safety data in GO29383 in 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 preferred terms (PTs): 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 FL. Atezolizumab + obinutuzumab demonstrated encouraging signs of response in heavily pretreated and refractory patients with relapsed/refractory FL. The ORR at the end of induction assessment (Lugano 2014 Response Criteria by PET-CT) was 56.5%, with a CR rate of 26.1%. The median duration of response and median PFS at time of clinical cutoff were 15.0 and 15.1 months, respectively. Although preliminary, these data may support the hypothesis that the addition of obinutuzumab to atezolizumab has the potential to reduce the incidence of autoimmune side effects observed with atezolizumab monotherapy by depleting B cells.

Clinical activity of lenalidomide has been demonstrated in the treatment of both relapsed or refractory indolent and aggressive NHL as a single agent (Wiernik et al. 2008; Witzig et al. 2011) and in combination with rituximab (see Section 1.1).

Obinutuzumab in combination with lenalidomide is currently being evaluated in an ongoing Phase Ib/II study sponsored by the Lymphoma Academic Research

Organisation (Study MO28005 [GALEN]) in patients with relapsed or refractory FL and aggressive lymphoma (DLBCL and mantle cell lymphoma), and supported by Roche in the form of an investigator-initiated study model. The recommended dose of lenalidomide was established at 20 mg/day on the basis of an increased incidence of Grade 3 or 4 neutropenia between Cycles 2 and 6 at the next higher dose of 25 mg/day (Morschhauser et al. 2014). The most common (occurring in ≥20% patients) adverse events observed during the dose escalation phase (all grades) in the 19 patients were neutropenia and constipation (10; 53% each), asthenia and upper respiratory tract infection (7; 37% each), rash/cutaneous eruption and cough (5; 26% each), and diarrhea and fever (4; 21% each). The only Grade 3 or 4 adverse event that occurred in 2 or more patients was neutropenia (8/19; 42%). IRRs occurred in 3 patients and did not exceed Grade 2. Preliminary efficacy data available from the dose-escalation phase of the study are encouraging, with an overall response according to Cheson 1999 criteria of 68% (13 of 19 evaluable patients), including 7 patients with a CR; 3 patients with a CR, unconfirmed; and 3 patients with a PR (Morschhauser et al. 2014).

The Phase II portion of the GALEN study is currently ongoing. Data for the 89 patients enrolled in the relapsed/refractory FL cohort (cutoff date: 22 November 2016) were presented at the 14th ICML conference (Morschhauser et al. 2017). The expansion phase at 20 mg/day of lenalidomide for the first-line FL cohort is currently in progress. Eighty-eight patients with relapsed/refractory FL were evaluable for safety and 86 for efficacy. With a median follow-up of 18.1 months, 75 patients (87.2%) completed induction and 67 (78%) entered maintenance. The median induction treatment duration was 5.3 months (0.2–6.7), with a median number of cycles received of 5.4 (1–6). The median dose intensity for both drugs was >98% during induction.

Preliminary results from the GALEN study suggest that the addition of lenalidomide to obinutuzumab represents an effective and safe combination in patients with relapsed or refractory FL. The overall response according to Cheson 2007 criteria was 74% (CR/CRu rate of 44%) and the 1-year PFS rate was 75.5% (95% CI: 64.2-83.7). The most common adverse events (>20% of patients) during induction (all grades) were gastrointestinal disorders (76%), infections (63%), asthenia (52%), neutropenia (31%), muscle spasms (30%), and cough (21%). The most common Grade 3/4 adverse events were infections (7%) and neutropenia (28%). Febrile neutropenia occurred in 3.4% of patients. Six second primary malignancies were reported in 3 patients (5 basal carcinoma and 1 myelodysplastic syndrome), and there were 3 fatal adverse events reported (3.4%): febrile neutropenia, pneumonia, and atypical pneumonia.

Currently available data continue to provide a strong rationale for an improved benefit-risk ratio with the addition of atezolizumab to the combination of obinutuzumab and lenalidomide in patients with FL. Strengthening the immunotherapy component of the combination is expected to result in deeper and long-lasting anti-tumor responses. Additionally, overlapping toxicities are expected to be manageable in the clinical setting and drug–drug interactions (DDIs) are unlikely to occur (see Section 5.1.4).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of induction treatment consisting of atezolizumab in combination with obinutuzumab plus lenalidomide (Atezo+G+Len) in patients with relapsed or refractory FL, followed by maintenance treatment with Atezo+G+Len in patients who achieve a CR, a PR, or stable disease 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 OBJECTIVES

The safety objectives for this study are as follows:

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

  Incidence of DLTs during Cycle 2 of study treatment

- To evaluate the safety and tolerability of Atezo+G+Len 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

2.2 EFFICACY OBJECTIVES

Response will be determined through use of the PET-CT scans or CT scans alone, using Revised Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014; see Appendix 3), hereinafter referred to as Lugano 2014 criteria. 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 Atezo+G+Len on the basis of the following endpoint:

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

2.2.2 Secondary Efficacy Objectives

The secondary efficacy objective for this study is to evaluate the efficacy of induction and maintenance treatments with Atezo+G+Len on the basis of the following endpoints:

- CR at EOI as determined by the investigator on the basis of PET-CT scans
- CR at EOI as determined by the IRC and by the investigator on the basis of CT scans alone

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

2.2.3 Exploratory Efficacy Objectives

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of Atezo + G + Len 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 on the basis of PET-CT scans
- PFS, defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by the investigator on the basis of CT scans alone or death from any cause
- Event-free survival (EFS), defined as the time from initiation of study treatment to any treatment failure, including disease progression or relapse, as determined by the investigator on the basis of CT scans alone; initiation of new anti-lymphoma therapy; or death from any cause, whichever occurs first
- Disease-free survival (DFS), defined as the time from the first occurrence of a documented CR to relapse among patients achieving a CR, as determined by the investigator on the basis of CT scans alone or death from any cause, whichever occurs first
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to the time of disease progression or relapse, as determined by the investigator on the basis of CT scans alone or death from any cause, whichever occurs first.
- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause

2.3 PHARMACOKINETIC OBJECTIVE

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

- Observed serum obinutuzumab concentration at specified timepoints
- Observed serum atezolizumab concentration at specified timepoints
- Observed plasma lenalidomide concentration at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab 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 anti-therapeutic antibodies to atezolizumab during the study relative to the prevalence of anti-therapeutic antibodies at baseline

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

- Correlation between HAHA or anti-therapeutic antibody status and efficacy, safety, or PK endpoints

2.5 BIOMARKER OBJECTIVE

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

- Association between non-inherited biomarkers (listed in Section 4.5.7) and efficacy, safety, 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, dose-escalation study will evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of Atezo+G+Len in patients with relapsed or refractory FL. The study will include an initial dose-escalation phase designed to determine the RP2D for lenalidomide in this treatment combination (see Section 3.1.2) followed by an expansion phase in which lenalidomide will be given at the RP2D (see Section 3.1.3). All patients will receive induction treatment with Atezo+G+Len for six cycles. Patients achieving a CR, a PR, or stable disease at EOI will be eligible to receive extended dosing of Atezo+G+Len as maintenance treatment (refer to Sections 3.1.2.2 and 3.1.3 for details on treatment regimens). A study schema is provided in Figure 1.

Overall, it is planned to have approximately 46 patients enrolled in this study at approximately 15 investigative sites around the world, mainly in Europe and North America.

All patients will be closely monitored for adverse events throughout the study and for at least 35 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 for Adverse Events (NCI CTCAE) v4.0. An Internal Monitoring Committee (IMC) will be established to monitor patient safety throughout the study (see Section 3.1.4).

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

Response will be determined by the IRC (see Section 3.1.5) and the investigator using the Lugano 2014 criteria (see Appendix 3). The primary efficacy endpoint will be based on IRC assessment of response. Refer to Section 4.5.5 for details on tumor assessments.

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

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

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

3.1.2 Dose-Escalation Phase

The purpose of the dose-escalation phase is to identify the RP2D for lenalidomide when combined with fixed doses of obinutuzumab and atezolizumab as induction treatment (see Section 3.3.1).

Approximately 6–12 patients will be enrolled in the dose-escalation phase. Dosing groups of 3–6 patients each will be treated in accordance with the treatment regimens and the dose-escalation rules described in Section 3.1.2.2.

Patients will be closely monitored for adverse events during a DLT assessment window, defined as Cycle 2. Adverse events meeting the criteria for DLT, as defined below (see Section 3.1.2.1), will be reported to the Sponsor within 24 hours (see Section 5.4.2).

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and for RP2D assessments and will be replaced by an additional patient at that same dose level. Patients who miss one or more doses of atezolizumab or obinutuzumab or five consecutive daily doses of lenalidomide during the DLT assessment window for reasons other than a DLT will also be replaced.

3.1.2.1 Definition of Dose-Limiting Toxicity

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

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

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

  Grade 4 neutropenia lasting >7 days

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

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

  Grade 3 or 4 IRRs

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

  Grade 3 diarrhea that responds to therapy within 72 hours

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

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

3.1.2.2 Treatment Regimens and Dose-Escalation Rules

A 3+3 dose-escalation schema will be used. Induction treatment will be administered in 28-day cycles, as outlined in Table 1. Obinutuzumab and atezolizumab will remain at fixed doses during the dose-escalation phase. For induction treatment, the starting dose for lenalidomide is 15 mg, which is one dose level below 20 mg, the RP2D identified for lenalidomide when given in combination with obinutuzumab in a Phase Ib/II study

(MO28005 [GALEN]). If the 15-mg dose is safe and tolerable, the lenalidomide dose will be escalated to 20 mg. Intrapatient dose escalation is not allowed.

Table 1 Induction Treatment for Dose-Escalation Phase

Cycle(s)	Atezo + G + Len (28-Day Cycles)
1	• Lenalidomide 15 or 20 mg [a] PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Days 1, 8, and 15
2–6	• Lenalidomide 15 or 20 mg [a] PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Day 1 • Atezolizumab 840 mg IV on Days 1 and 15

IV = intravenous; PO = by mouth.

[a] Dose may be de-escalated to 10 mg.

Dose escalation will occur in accordance with the rules listed below.

First Dosing Group (15 mg of Lenalidomide)

- A minimum of 3 patients will initially be enrolled in the first dosing group (15 mg of lenalidomide). Patients within the dosing group may be treated in parallel.
- If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the second dosing group (i.e., 20 mg of lenalidomide) may proceed.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the dosing group will be expanded to at least 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the second dosing group may proceed.
- If 2 or more of the first 3 DLT-evaluable patients experience a DLT, the RP2D will have been exceeded, and dose escalation will stop. The Medical Monitor, in discussion with the Principal Investigator and participant investigators, may decide to proceed with dose de-escalation and enroll patients at 10 mg of lenalidomide, following the same 3 + 3 design.
- If 2 or more of the first 6 DLT-evaluable patients experience a DLT, the RP2D will have been exceeded, and dose escalation will stop. The Medical Monitor, in discussion with the Principal Investigator and participant investigators, may decide to proceed with dose de-escalation and enroll patients at 10 mg of lenalidomide, following the same 3 + 3 design.

Second Dosing Group (20 mg of lenalidomide)

- A minimum of 3 patients will initially be enrolled in the second dosing group (20 mg of lenalidomide). Patients within the dosing group may be treated in parallel.
- If none of the first 3 DLT-evaluable patients experiences a DLT, the dosing group will be expanded to 6 patients to confirm the dose of 20 mg as the RP2D for lenalidomide.

- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the dosing group will be expanded to at least 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, 20 mg will be declared the RP2D for lenalidomide.
- If 2 or more of the first 3 DLT-evaluable patients experience a DLT, the RP2D will have been exceeded, and 15 mg will be declared the RP2D for lenalidomide.
- If 2 or more of the first 6 DLT-evaluable patients experience a DLT, the RP2D will have been exceeded, and 15 mg will be declared the RP2D for lenalidomide.

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

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

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

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

Patients who achieve a CR, a PR, or stable disease at EOI may receive maintenance treatment with Atezo$+$G$+$Len, as outlined in Table 3. Maintenance treatment should start 8 weeks ($\pm$1 week) after Day 1 of Cycle 6 and will continue until disease progression or unacceptable toxicity for up to 24 months.

3.1.3 Expansion Phase

The expansion phase is designed to further assess the safety and efficacy of the combination of atezolizumab with obinutuzumab plus lenalidomide when given as induction and maintenance treatment.

Approximately 40 patients with FL will be enrolled during the expansion phase and treated as described below. Patients who received lenalidomide at the RP2D during the dose-escalation phase will be pooled with patients treated in the expansion phase. All patients will receive induction treatment as outlined in Table 2.

Table 2 Induction Treatment for Expansion Phase

Cycle(s)	Atezo + G + Len (28-Day Cycles)
1	• Lenalidomide at RP2D PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Days 1, 8, and 15
2–6	• Lenalidomide at RP2D PO once daily on Days 1–21 • Obinutuzumab 1000 mg IV on Day 1 • Atezolizumab 840 mg IV on Days 1 and 15

IV = intravenous; PO = by mouth; RP2D = recommended Phase II dose.

Patients who achieve a CR, a PR, or stable disease at EOI will receive maintenance treatment with Atezo + G + Len, as outlined in Table 3. Maintenance treatment should start 8 weeks (± 1 week) after Day 1 of Cycle 6 and will continue until disease progression or unacceptable toxicity for up to 24 months.

Table 3 Maintenance Treatment

Patients with FL	Maintenance treatment consisting of the following, administered for 24 months (from Months 1–24 [a]): • Lenalidomide 10 mg PO once daily on Days 1–21 of each month for a maximum of 12 months • Obinutuzumab 1000 mg IV on Day 1 of every other month (i.e., every 2 months), starting with Month 1 • Atezolizumab 840 mg IV on Days 1 and 2 of each month

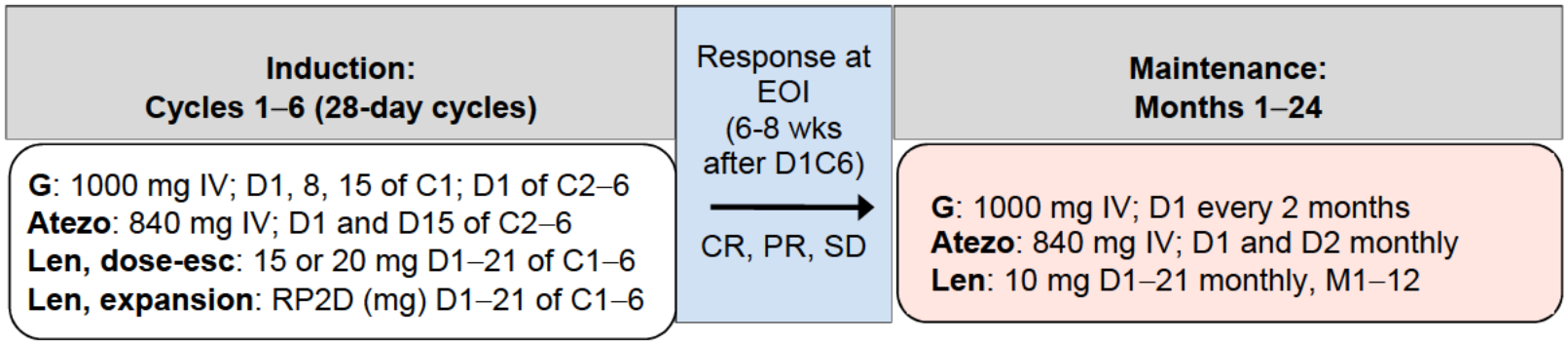
FL = follicular lymphoma; IV = intravenous; PO = by mouth.

[a] 1 month = 28 days.

In the event that any one of the stopping rules criteria (refer to Section 6.11 for further details) occurs at any time in the expansion phase, enrollment of patients will be paused while an IMC is immediately convened to review and provide a recommendation on further conduct of the study (e.g., consider study discontinuation).

A schedule of assessments is provided in Appendix 1, and a study schema is provided in Figure 1.

Figure 1 Study Schema



Atezo = atezolizumab; C = cycle; CR = complete response; D = day; D1C6 = Day 1 of Cycle 6; EOI = end of induction; FL = follicular lymphoma; G = obinutuzumab; IV = intravenous; Len = lenalidomide; M = month; PO = by mouth; QD = once daily; PR = partial response; RP2D = recommended Phase II dose; SD = stable disease.

[a] Lenalidomide dose may be de-escalated to 10 mg during the dose-escalation phase.

[b] Maintenance treatment should start 8 weeks (±1 week) after Day 1 of Cycle 6.

3.1.4 Internal Monitoring Committee

An IMC will monitor patient safety throughout the study. The IMC will include the Sponsor representatives from Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis. In addition to the ongoing assessment of the incidence and nature of adverse events (particularly, Grade ≥3 events), serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review data supporting the determination of the RP2D and cumulative data at regular intervals, every 4 months for safety and efficacy, and ad-hoc if safety concerns arise between the planned regular 4-month intervals, during the expansion phase.

Predefined stopping rules for excess toxicity, including fatal adverse events, have been included in Section 6.11. In the event that any of the stopping rules criteria are met at any time during the course of the study, enrollment of patients will be paused while an IMC meeting is immediately convened to review and provide a recommendation on further conduct of the study (e.g., consider study discontinuation).

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 or discontinued the maintenance treatment, 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, members' roles and responsibilities, and data to be reviewed will be detailed in an IMC charter.

3.1.5 Independent Review Committee

An IRC will assess all patients for response on the basis of imaging results and bone marrow biopsy results. 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.

3.1.6 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 be evaluated for survival status and initiation of new anti-lymphoma treatment every 3 months until the end of the study. Details are provided in the schedule of assessments (see Appendix 1).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the time when all enrolled patients have completed or discontinued study treatment (including induction treatment and maintenance treatment as applicable).

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

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

As discussed in Section 1.1, despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, FL remains essentially an incurable disease. Patients ultimately relapse, and subsequent active and well-tolerated agents are needed. The combination of lenalidomide with rituximab has shown promising results in Phase II clinical trials in patients with relapsed or refractory FL, with an overall response and a CR of 74%–75% and 32%–44%, respectively (Leonard et al. 2012; Tuscano et al. 2014) and an mPFS of 16.2 months (Tuscano et al. 2014).

On the basis of the biologic and clinical rationale presented in Section 1.4, the addition of atezolizumab to obinutuzumab and lenalidomide is a promising approach to expand the number of patients with relapsed or refractory FL who achieve remission and to decrease the relapse rate in these patients.

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:
1) 840 mg Q2W (840 mg on Days 1 and 15 of Cycles 2–6, given in 28-day cycles with G-Len as induction treatment) or 2) 1680 mg every 4 weeks (Q4W) (840 mg on Days 1 and 2 of each month, given with G-Len as maintenance treatment. Both dosages are equivalent to an average body weight–based dose of 15 mg/kg Q3W.

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

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including the following:
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 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 during the dose-expansion stage. Anti-tumor activity has been observed across all dose cohorts. There was no evidence of dose-dependent toxicity in this study. The MTD of atezolizumab was not reached, and no DLTs were observed at any dose. Anti-therapeutic antibodies 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 anti-therapeutic antibodies. To date, no relationship has been observed between the development of measurable anti-therapeutic antibodies and safety or efficacy. After review of available PK and anti-therapeutic antibody 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 anti-therapeutic antibodies that could lead to subtherapeutic levels of atezolizumab.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight–adjusted dose. On the basis of this analysis, a fixed dose of 1200 mg Q3W (equivalent to a weight-based dose of 15 mg/kg Q3W) was defined as the RP2D.

For the 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 concentration-time curve (AUC) would be comparable to that of 1200 mg Q3W (data available on request). The current manufacturing process considers 1200 mg the maximum daily dose for clearance of manufacturing process-derived impurities (such as host-cell DNA and endotoxins) to safe levels. 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, the total dose of 1680 mg will be split into two daily doses to minimize the theoretical risk of exceeding safe limits.

In Study PCD4989g, atezolizumab was safely administered to 11 patients with various hematologic malignancies (including 7 patients with lymphoma) at doses of 15 mg/kg Q3W ($n = 1$) or 20 mg/kg Q3W ($n = 10$). Atezolizumab 1200 mg Q3W is currently being evaluated in combination with obinutuzumab in an ongoing Phase Ib study (GO29383) in patients with relapsed or refractory DLBCL or FL (see Section 1.4.3.2). Atezolizumab is

added to obinutuzumab starting with Cycle 2 to avoid overlapping IRRs during the first infusion of obinutuzumab, which is known to be associated with the highest incidence and risk of severe IRRs. The combination has been safely administered in the first 6 patients who were evaluable for DLTs. Consistent with the dosing schedule used in Study GO29383, in this study, atezolizumab will be added to G-Len starting with Cycle 2.

3.3.2.2 Rationale for Obinutuzumab and Lenalidomide Dose and Schedule

Obinutuzumab in combination with lenalidomide is currently being evaluated in an ongoing Phase Ib/II study (MO28005 [GALEN]) in patients with relapsed or refractory FL and aggressive lymphoma (DLBCL and mantle cell). A total of 20 patients with relapsed or refractory FL have been enrolled in the dose-escalation phase of the study and have received escalating doses of oral lenalidomide ranging from 10 to 25 mg/day on Days 1–21 of a 28-day cycle in combination with obinutuzumab at a fixed dose of 1000 mg on Days 8, 15, and 22 of Cycle 1 and on Day 1 of Cycles 2–6. The RP2D of lenalidomide was established as 20 mg/day on the basis of an increased incidence of Grade 3 or 4 neutropenia between Cycles 2 and 6 at the next higher dose of 25 mg/day (Morschhauser et al. 2014). The enrollment in the expansion phase at 20 mg/day is in progress. As of 30 September 2014, 45 patients were evaluable for safety during induction treatment (Cycles 1–6). Preliminary data demonstrate a manageable safety profile (see Section 1.4.3.2). In this study, the starting dose for lenalidomide during induction treatment is 15 mg/day on Days 1–21 of a 28-day cycle, which is one dose level below the RP2D of 20 mg/dose defined in Study MO28005 (GALEN).

During maintenance treatment, the lenalidomide dose will be 10 mg/day on Days 1–21, every month for 12 months. The use of lenalidomide at this dosing regimen in the maintenance setting in lymphoma is currently being evaluated in ongoing Phase Ib/II and Phase III studies in patients with FL, both as a single agent (e.g., RELEVANCE ClinicalTrial.gov, number NCT01476787) and in combination with obinutuzumab (Study MO28005 [GALEN]). The proposed dosing regimen for lenalidomide as maintenance treatment is also supported by the available clinical data from randomized studies in multiple myeloma that evaluate lenalidomide maintenance in patients following stem-cell transplantation (Attal et al. 2013; McCarthy et al. 2012) and in patients ineligible for transplantation (Palumbo et al. 2012). Results from these studies demonstrate a favorable benefit-risk profile of lenalidomide 10-mg maintenance therapy, allowing for continuous long-term treatment in this setting.

3.3.2.3 Rationale for Treatment Duration

In this study, patients with relapsed or refractory FL will receive six cycles of induction treatment followed by extended dosing with Atezo+G+Len as maintenance treatment in patients who achieve a CR, a PR, or have stable disease at the EOI.

Despite recent improvements in therapy for FL, including demonstrated benefit from 2-year rituximab maintenance in patients responding to first-line immunochemotherapy

(Study MO18264), FL is still not considered curable, with a 6-year PFS of 59.2% (Salles et al. 2013). A Phase III study, GAO4753g, investigated obinutuzumab plus bendamustine (GB) compared with bendamustine alone in patients with rituximab-refractory iNHL (n = 396). Patients in the GB 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, demonstrating significant improvement in PFS in the GB arm, with a median PFS of 29 versus 14 months (HR: 0.52; 95% CI: 0.39, 0.70; p 0.0001) (Sehn et al. 2015), the Independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor. These data support further investigation of obinutuzumab in combination with new targeted drugs in the setting of induction and maintenance treatment for patients with FL.

The objective of maintenance treatment is to improve the response to induction therapy, either by improving the quality of clinical response (e.g., converting a PR to a CR) or by eradicating minimal residual disease (MRD) to achieve a molecular response, thus reducing the relapse risk. In this study, MRD levels will be measured during the maintenance period as an additional means of evaluating the benefits of the triple combination as a maintenance treatment. On the basis of the nonclinical rationale (presented in Section 1.4.3.1), it is hypothesized that the addition of atezolizumab and lenalidomide to obinutuzumab may enhance and prolong the anti-tumor immune response and provide significant clinical benefit to patients.

In the ongoing Phase Ib/II Study MO28005 (GALEN), evaluating the combination of obinutuzumab and lenalidomide in patients with relapsed or refractory FL, maintenance treatment consists of obinutuzumab administered every 2 months for 2 years and lenalidomide administered on Days 1–21 of each 28-day cycle for 1 year. Building upon this basis, the same obinutuzumab and lenalidomide dosing schedule will be employed in this study. Nonclinical data demonstrating synergism between obinutuzumab and atezolizumab, associated with a low risk of overlapping toxicities, provide the rationale for administering atezolizumab as maintenance treatment on a monthly basis for the same period of 2 years.

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

In DLBCL, the prognostic value of the post-treatment fluorodeoxyglucose (FDG) PET-CT scan has been well documented (Thomas et al. 2010; Vitolo et al. 2010). PET-CT scans have been implemented in the Lugano 2014 criteria (Cheson et al. 2014) and are commonly used to assess efficacy in medical practice and clinical trials in lymphoma. More recently, the value of post-induction PET-CT status has been investigated as a prognostic marker for long-term outcome in patients with FL. In the first-line setting, results from a pooled analysis of 246 patients enrolled in three studies and having PET-CT scans available at the end of chemoimmunotherapy showed, with a median follow-up of 55 months, a 4-year PFS in PET-CT–positive and PET-CT–negative

patients of 23.2% (95% CI: 11.1%, 37.9%) versus 63.4% (95% CI: 55.9%, 70.0%; $p < 0.001$), respectively, and a 4-year survival of 87.2% (95% CI: 71.9%, 94.5%) versus 97.1% (95% CI: 93.2%, 98.8%; $p < 0.0001$), respectively (Trotman et al. 2014). In the relapsed FL setting, results from the preliminary analysis of a 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 patients compared with that in 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 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 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. 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 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., 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 value of soluble PD-L1 in FL is unknown. Soluble PD-L1 levels at baseline will be assessed in this study to support an exploratory biomarker analysis. Any correlation with PK parameters may also be examined.

DLBCL subtypes (Activated B-cell, ABC and Germinal Centre B-cell) have been shown to be prognostic (Alizadeh et al. 2000). Furthermore, a subtype specific activity of lenalidomide in ABC DLBCL has been reported (Nowakowski et al. 2015). Therefore, DLBCL subtypes will be determined in the study.

Similarly, expression of Bcl-2 and concomitant Bcl-2 and Myc was shown to be prognostic (Johnson et al. 2012). To understand the prevalence and impact of upregulated expression of Bcl-2 and Bcl-2/Myc, these markers will be assessed.

3.3.4.2 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 circulating tumor DNA can be detected and quantified at low levels as MRD to assess depth of response and to monitor patients for possible disease recurrence.

In FL, MRD at end of treatment is likely to be prognostic (Ladetto et al. 2013).
In addition, MRD assessment may complement the response assessment, particularly in immune treatment–based regimens, and mitigate potential false-positive PET-CT results caused by infiltration of metabolically active immune cells into the tumor.

In this study, MRD will be quantified by circulating lymphoma cells and circulating tumor DNA as an exploratory endpoint. The lymphoma clone will be identified in DNA from the lymphoma tissue specimen. MRD levels will be determined in blood samples collected prior to dosing and during treatment to explore a pharmacodynamic relationship. MRD assessments will be performed at the EOI to allow for an evaluation of the depth of response and during maintenance treatment to allow for an evaluation of long-term response or possible disease recurrence.

4. MATERIALS AND METHODS

4.1 PATIENTS

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

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years
- ECOG Performance Status of 0, 1, or 2 (see Appendix 4)
- Relapsed or refractory FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator

- 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

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

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

  Further details are provided in Section 4.5.7.
- Agreement to comply with all local requirements of the lenalidomide risk minimization plan

  In every country where lenalidomide has been approved, a risk minimization plan, which includes a pregnancy prevention program, is in place. The risk minimization plan should be followed by patients using lenalidomide.
  In addition, because lenalidomide will be administered in combination with atezolizumab and obinutuzumab, patients must comply with contraceptive measures designed to ensure safe administration of all three study treatments, as outlined below.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of <1% per year, for at least 28 days prior to Day 1 of Cycle 1, during the treatment period (including periods of treatment interruption), and for at least 18 months after the last dose of study treatment

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

  Examples of non-hormonal contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established and proper use of progestogen-only hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. Combined oral contraceptives are not recommended because of the increased risk of venous and arterial thromboembolism (TE) in patients taking lenalidomide.

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

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 or 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 to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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:

- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Known CD20-negative status at relapse or progression
- CNS lymphoma or leptomeningeal infiltration
- Prior allogeneic SCT
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1
- History of resistance to lenalidomide or response duration of <1 year (for patients who had a response to a prior lenalidomide-containing regimen)
- Prior standard or investigational anti-cancer therapy as specified below:

  Lenalidomide, fludarabine, or alemtuzumab within 12 months prior to Day 1 of Cycle 1

  Radioimmunoconjugate within 12 weeks prior to Day 1 of Cycle 1

  Monoclonal antibody or 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

  Anti–PD-1, anti–PD-L1, anti-CTLA4, anti–CD137/41-BB agonist, or anti-CD40 agonist antibodies
- Clinically significant toxicity (other than alopecia) from prior treatment that has not resolved to Grade ≤ 2 (per NCI CTCAE v4.0) prior to Day 1 of Cycle 1

- Treatment with systemic immunosuppressive medications, including, but not limited to, prednisone, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor agents within 2 weeks prior to Day 1 of Cycle 1

    Treatment with inhaled corticosteroids and mineralocorticoids is permitted.

    If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, 100 mg of prednisone or equivalent can be given for a maximum of 5 days, but all tumor assessments must be completed prior to initiation of corticosteroid treatment.
- History of solid organ transplantation
- History of severe allergic or anaphylactic reaction to humanized, chimeric or murine monoclonal antibodies
- Known sensitivity or allergy to murine products
- Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab, obinutuzumab, or lenalidomide formulation, including mannitol
- History of erythema multiforme, Grade ≥ 3 rash, or blistering following prior treatment with immunomodulatory derivatives such as thalidomide and lenalidomide
- 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 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 progressive multifocal leukoencephalopathy
- 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:

    Any of the following malignancies, previously curatively treated: carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, or basal or squamous cell skin cancer

Stage I melanoma, low-grade; early-stage localized prostate cancer; or any other previously treated malignancy that has been in remission without treatment for ≥5 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 8 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.

- Contraindication to treatment for TE prophylaxis (see Section 4.3.2.6)
- Grade ≥2 neuropathy
- 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
- 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):

  Calculated creatinine clearance <60 mL/min (using the Cockcroft-Gault formula; see Appendix 9)

  AST or ALT >2.5 times the upper limit of normal (ULN)

  Serum total bilirubin >1.5×ULN (or >3×ULN for patients with Gilbert syndrome)

  INR or PT >1.5×ULN in the absence of therapeutic anticoagulation

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

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

  Women of childbearing potential must have two negative serum pregnancy test results (minimum sensitivity, 25 mIU/mL) prior to initiating therapy: at 10−14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1.
- Life expectancy <3 months
- Unable to comply with the study protocol, in the investigator's judgment

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study of Atezo+G+Len in patients with relapsed or refractory FL. During the dose-escalation phase, an interactive voice or web-based response system (IxRS) will be used to assign patients to dosing groups that vary according to the dose of lenalidomide given during induction treatment. During the expansion phase, patients will receive lenalidomide at the RP2D during induction treatment. All patients will receive lenalidomide at a dose of 10 mg during maintenance treatment. Atezolizumab and obinutuzumab will be given at stable doses to all patients, during both induction and maintenance treatment.

Enrollment tracking will be performed through use of the IxRS. Prior to initiating screening, the study site should confirm via the IxRS that slots are available for enrollment. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves the patient for enrollment, the patient number will be assigned and the patient will be enrolled via the IxRS. The Sponsor will communicate to the sites impending closure of screening.

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/40 mL of obinutuzumab. In addition to the drug substance, the liquid is also composed of histidine, trehalose, and poloxamer 188. For information on the formulation and handling of obinutuzumab, see the obinutuzumab Investigator's Brochure and the Pharmacy Manual.

4.3.1.2 Atezolizumab

Atezolizumab will be supplied by the Sponsor as an IMP. Atezolizumab drug product is formulated as 60 mg/mL of atezolizumab in 20 mM histidine acetate, 120 mM sucrose, pH 5.8 with 0.04% (w/v) polysorbate 20. Atezolizumab is provided in a single-use, 20-mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed

to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume. Extraction of 14 mL of atezolizumab solution will contain an 840-mg dose. For information on the formulation and handling of atezolizumab, see the Atezolizumab Investigator's Brochure and the Pharmacy Manual.

4.3.1.3 Lenalidomide

Lenalidomide will be supplied by the Sponsor as an IMP. Lenalidomide will be provided as 5-, 10-, 15-, and 20-mg capsules.

Female caretakers of patients taking lenalidomide who are of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves. Lenalidomide should be stored at room temperature away from direct sunlight and should be protected from excessive heat and cold.

For information on the formulation and handling of lenalidomide, see the local prescribing information for lenalidomide.

4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized in Table 4 and Table 5 (see Sections 4.3.2.4 and 4.3.2.5).

Premedication and treatment for TE prophylaxis should be administered as described in Section 4.3.2.6.

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

4.3.2.1 Obinutuzumab

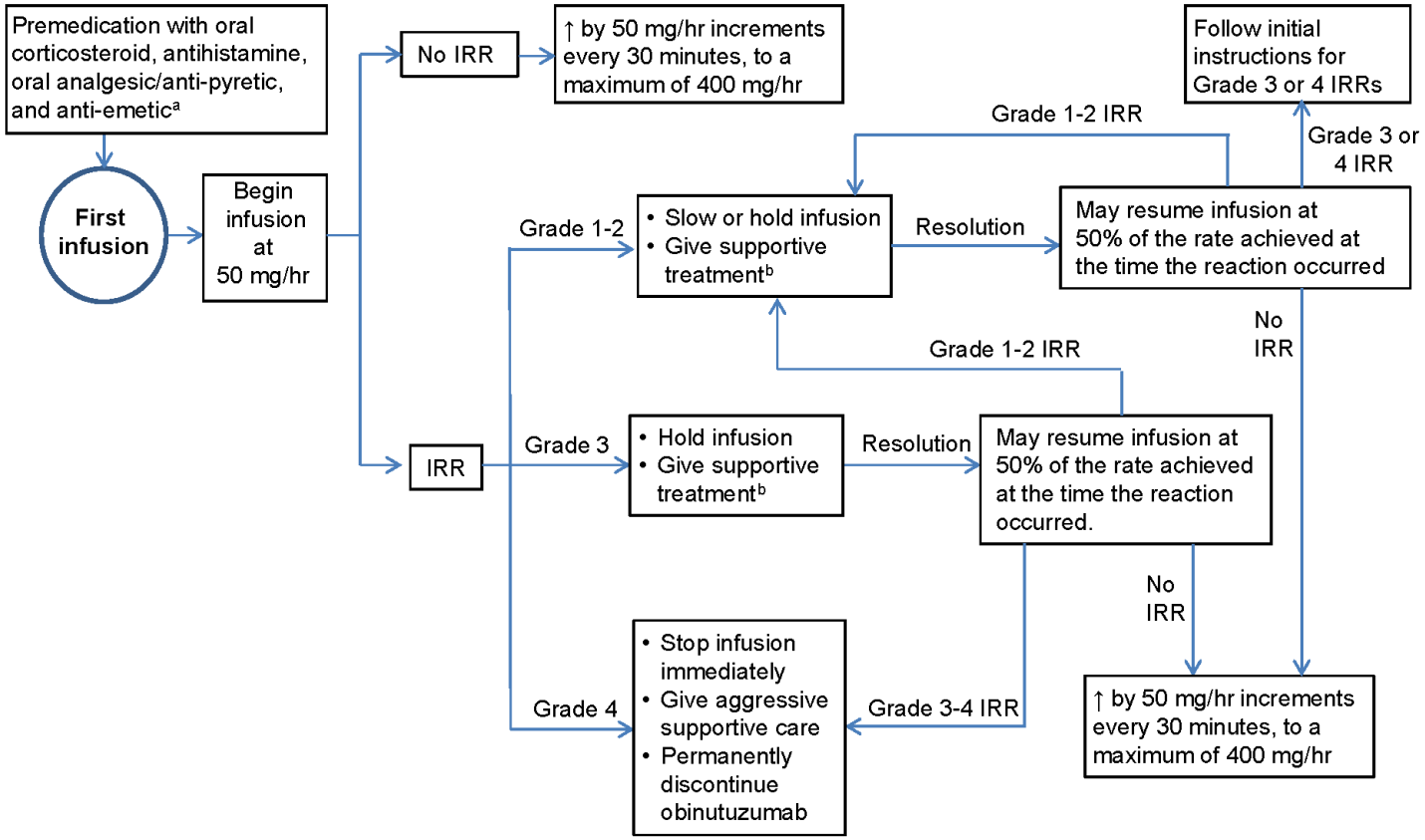
Obinutuzumab will be administered by IV infusion at an absolute (flat) dose of 1000 mg on Days 1, 8, and 15 of the first cycle and on Day 1 of each subsequent cycle during induction treatment, and on Day 1 of every other month (i.e., every 2 months) during maintenance treatment.

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

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

Premedication with a corticosteroid, analgesic/antipyretic, and antihistamine, as outlined in Section 4.3.2.6 (see Table 6), is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 7.

Figure 2 Guidelines for Obinutuzumab Infusions: First Infusion

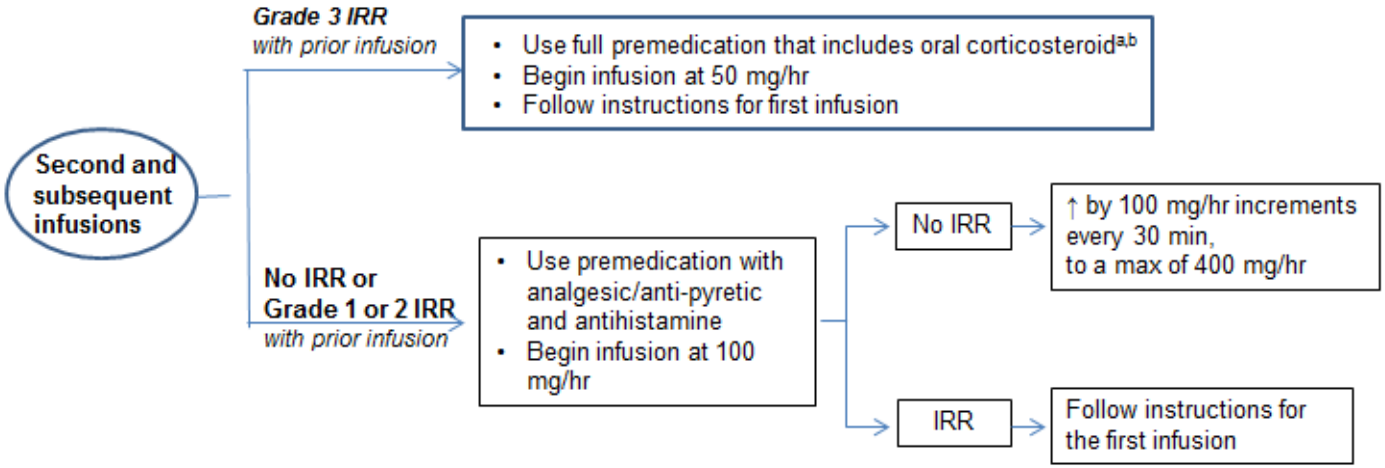


IRR = infusion-related reaction.

[a] All patients should receive full premedication with an oral corticosteroid, oral analgesic/anti-pyretic, and antihistamine prior to the first obinutuzumab infusion. Refer to Section 4.3.2.6 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 7.

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 4.3.2.6 for details. In the case of a recurrent Grade 3 IRR, obinutuzumab may be discontinued at the discretion of the investigator, following an individual benefit-risk assessment.

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

4.3.2.2 Atezolizumab

Atezolizumab will be administered at a flat dose consisting of one of the following: a) 840 mg Q2W (840 mg on Days 1 and 15 of Cycles 2–6, given in 28-day cycles as induction treatment) and b) 1680 mg Q4W (840 mg on Days 1 and 2 of each month, given as maintenance treatment). Detailed atezolizumab dosing regimens are provided in Table 4 for induction treatment and in Table 5 for maintenance treatment (see Sections 4.3.2.4 and 4.3.2.5).

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 and aggressive resuscitation and supportive measures should be initiated. In the event of a life-threatening IRR, atezolizumab should be permanently discontinued.

For anaphylaxis precautions, see Appendix 7.

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

4.3.2.3 Lenalidomide

Lenalidomide will be administered orally once daily on Days 1–21 of Cycles 1–6 (28-day cycles) during induction treatment and on Days 1–21 of each month during maintenance treatment. During the dose-escalation phase, lenalidomide will be administered at a dose of 15 or 20 mg (dose may be de-escalated to 10 mg) during induction treatment and at 10 mg during maintenance treatment. During the expansion phase, lenalidomide will be administered at the RP2D during induction treatment and at 10 mg during maintenance treatment.

Lenalidomide capsules should be swallowed whole with water and should not be broken, chewed, or opened. The capsules may be taken with or without food, except on

lenalidomide PK sampling days (see Appendix 2), when the patient should fast (water allowed) at least 2 hours before and at least 1 hour after the lenalidomide dose. On lenalidomide PK sampling visits, lenalidomide dose will be taken in the clinic.

Lenalidomide should be administered at approximately the same time each day. If a dose of lenalidomide is missed and it has been <12 hours since the time of the scheduled dose, the patient may take the missed dose. If it has been >12 hours, the dose should be skipped and the next dose should be taken at the regularly scheduled time. Two doses should not be taken at the same time. If a dose had been vomited, the dose should not be re-taken.

At each cycle, each patient will be supplied with only enough lenalidomide for that cycle. A drug diary will be provided to the patient to record oral administration of doses, including the date and time. Patients will be instructed to return empty bottles or unused capsules. The investigator is responsible for monitoring patient compliance by monitoring the patient diary and counting unused capsules.

4.3.2.4 Induction Treatment with Atezolizumab, Obinutuzumab, and Lenalidomide (Atezo+G+Len)

Patients will receive induction treatment, administered in 28-day cycles as follows:

- Patients will receive six cycles of induction treatment consisting of obinutuzumab and lenalidomide for Cycles 1–6 and atezolizumab for Cycles 2–6 as outlined in Table 4.

Lenalidomide may be administered before or concomitantly with obinutuzumab. After completion of the obinutuzumab infusion, the line will be flushed (unless there is a central line with more than one line/port), after which atezolizumab will be administered.

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

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

Table 4 Induction Treatment

Treatment	Dose	Route	Regimen (28-Day Cycles)	
			Cycle 1	Cycles 2–6
Lenalidomide	Dose-escalation phase: 15 or 20 mg [a] Expansion phase: RP2D	PO	Days 1–21	Days 1–21
Obinutuzumab	1000 mg	IV	Days 1, 8, and 15	Day 1
Atezolizumab	840 mg	IV	—	Days 1 and 15

IV = intravenous; PO = by mouth; RP2D = recommended Phase II dose.

[a] Dose may be de-escalated to 10 mg.

4.3.2.5 Maintenance Treatment with Atezolizumab, Obinutuzumab, and Lenalidomide (Atezo + G + Len)

Patients who achieve a CR, a PR, or stable disease at EOI are eligible for maintenance treatment with atezolizumab and obinutuzumab for 24 months and lenalidomide for 12 months, as outlined in Table 5.

Lenalidomide will be given before other agents are administered on the same day. Obinutuzumab will be administered next, followed by a line flush (unless there is a central line with more than one line/port), after which atezolizumab will be administered.

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

Table 5 Maintenance Treatment

Treatment	Dose	Route	Regimen (Months 1–24)
Lenalidomide	10 mg	PO	Days 1–21 of each month for a maximum of 12 months
Obinutuzumab	1000 mg	IV	Day 1 of every other month (i.e., every 2 months), starting with Month 1
Atezolizumab	840 mg	IV	Days 1 and 2 of each month

IV = intravenous; PO = by mouth.

4.3.2.6 Premedication and Other Prophylaxis Treatment

Patients should receive premedication as outlined in Table 6.

Granulocyte colony-stimulating factor (G-CSF) may be administered in each cycle of therapy as primary prophylaxis for neutropenia, per American Society of Clinical Oncology, EORTC, and European Society for Medical Oncology guidelines (Smith et al. 2015) or per each site's institutional standards.

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

Lenalidomide increases the risk of TE. Anticoagulation prophylaxis should be given after a careful assessment of a patient's underlying risk factors. All patients will receive daily low-dose aspirin (81–100 mg) during lenalidomide treatment and until 28 days after the last dose of lenalidomide. Patients who are unable to tolerate aspirin, who have a history of TE, and who are at high risk of TE should receive warfarin or low-molecular-weight heparin (LMWH).

Table 6 Premedi cation

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

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

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

[b] For example, 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 (atezolizumab, obinutuzumab, and lenalidomide) 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 Atezolizumab and Obinutuzumab

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

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

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to the screening period to the visit at the EOI or at the end of maintenance (EOM) treatment, whichever occurs later. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Prophylaxis treatment and premedication should be administered as described in Section 4.3.2.6.

Patients who use oral contraceptives, hormone replacement therapy, or other maintenance therapy should continue their use. However, it must be noted that erythropoietic agents or other agents that may increase the risk of thrombosis, such as estrogen-containing therapies (e.g., oral contraceptives), are not recommended because of the increased risk of TE in patients taking lenalidomide. Suitable methods of contraception are presented in Section 4.1.1.

Patients using concomitant medication that could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants) may be at a greater risk of bleeding. When possible, replace prior vitamin K antagonist therapy with 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 CNS prophylaxis
- Hormonal therapy other than contraceptives, stable hormone replacement therapy, or megestrol acetate
- Biologic agents other than G-CSF (as described in Section 4.3.2.6)
- Immunostimulatory agents, including, but not limited to, interferon alpha, 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®) 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 until B-cell recovery.

4.5 STUDY ASSESSMENTS

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

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-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); 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 period and until the EOI or EOM visit, whichever occurs later, 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 4)
- B symptoms (unexplained fever $>38°C$, night sweats, unexplained weight loss $>10\%$ of body weight over 6 months)
- Ann Arbor staging (see Appendix 5)
- Follicular Lymphoma International Prognostic Index (FLIPI) and Follicular Lymphoma International Prognostic Index 2 (FLIPI2) (see Appendix 6)
- 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 on Cycle 1 Day 1 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 schedule of assessments (see Appendix 1), but the associated data, other than the data collected at screening, do not need to be recorded on the eCRF (except in the case of an adverse event as presented in Section 5.3.6.6).

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 PET and CT scans, using the Lugano 2014 criteria. In this study, the Lugano 2014 criteria for a PET-CT–based CR have been slightly modified to require normal bone marrow for patients with bone marrow involvement at screening. Additionally, 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 (see Appendix 3).

4.5.6 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 these allow consistent and precise measurement of the targeted lesions during the study treatment period.

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

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

4.5.6.1 Bone Marrow Assessments

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

If bone marrow infiltration is present at screening, a bone marrow biopsy is required at the EOI response assessment for all patients who may have achieved a CR. In patients with a PR at the EOI, a bone marrow examination may be required at a later timepoint during maintenance treatment or at the EOM to confirm a CR that was achieved after the EOI response assessment.

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

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Local Laboratory Assessments

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

- Hematology: hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)

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

  All women of childbearing potential must have two negative serum pregnancy test results (minimum sensitivity, 25 mIU/mL) prior to initiating therapy: at 10–14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1. Urine pregnancy tests will be performed at specified subsequent visits (see Appendix 1). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Viral serology

  Hepatitis B testing includes HBsAg and total HBcAb.

  Hepatitis C testing includes HCV antibody.
- Quantitative immunogloblulins: IgA, IgG, 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 PK analysis using a validated assay
- Plasma samples for lenalidomide PK analysis using a validated assay. Relevant biotransformation products of lenalidomide may also be analyzed at the discretion of the Sponsor.
- Serum samples for assessment of HAHAs to obinutuzumab using a validated assay
- Serum samples for assessment of anti-therapeutic antibodies to atezolizumab using validated assays
- Tumor tissue samples and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL, and for exploratory research on candidate biomarkers (see Table 7)

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

If the available biopsy was performed more than 12 months prior to Day 1 of Cycle 1, or the patient received anti-lymphoma treatment between the time of the most recent available biopsy and Day 1 of Cycle 1, a core-needle biopsy is strongly recommended.

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

Analysis methods will be detailed in the Biomarker Analysis Plan.

- Tumor biopsy samples obtained prior to the start of Cycle 2 and at the time of progression (unless no adequate tumor site is accessible) for exploratory research on candidate biomarkers (see Table 7)
- Serum samples for exploratory research on candidate biomarkers (see Table 7)
- Whole blood samples for exploratory research on candidate biomarkers (see Table 7)
- Whole blood samples for isolation of peripheral blood mononuclear cells for exploratory research on candidate biomarkers (see Table 7)

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 7.

Table 7 Proposed Non-Inherited Biomarkers

Sample Type	Timing	Proposed Non-Inherited Biomarkers
Archival or fresh tumor tissue	Prior to study (archival) or baseline (fresh)	• 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) • Cytokines, drug transporters, and genes related to regulation of apoptosis

Table 7 Proposed Non Inherited Biomarkers (cont.)

Sample Type	Timing	Proposed Non-Inherited Biomarkers
Tumor tissue biopsy	Prior to the start of Cycle 2 and at the time of progression (unless no adequate tumor site is accessible)	• Immune infiltrate, PD-L1, CD8 and other biomarkers of T-cell subpopulations, cytokines, drug transporters, and genes related to regulation of apoptosis
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)

HLA = 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).

4.5.8 Electrocardiograms

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

4.5.9 Samples for Roche Clinical Repository

4.5.9.1 Overview of the Roche Clinical Repository

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

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

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

4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR are contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board (IRB) or Ethics Committee (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 atezolizumab, obinutuzumab, 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 BO29562 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 BO29562.

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 <u>Patient Discontinuation</u>

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time

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

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

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

4.6.2 Study Treatment Discontinuation

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

- Anaphylaxis, acute respiratory distress, or Grade 4 IRR

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

- Disease progression

  Because of the potential for tumor flares with immunotherapies, resulting in early apparent radiographic progression (pseudoprogression/tumor immune infiltration), including the appearance of new lesions followed by delayed response (Wolchok et al. 2009), patients whose CT scans at the end of Cycle 2 meet criteria for disease progression may continue to receive study treatment at the discretion of the investigator and following discussion with the Medical Monitor, if certain criteria are met (see Section 3.1.4 for details). Cases of delayed pseudoprogression have also been described in patients with solid tumors treated with immunotherapies. In case of CT- findings suggestive for pseudoprogression in patients with persistent clinical benefit, the investigator should contact the Medical Monitor to discuss further patient management. Patients who continue to receive study treatment should have a CT scan repeated 4–8 weeks later.
- Pregnancy

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

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

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

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

4.6.3 Study and Site Discontinuation

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

- The incidence or severity of adverse events (see Section 6.11, Stopping Rules for Safety) 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 lenalidomide) 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 5.1.5).

5.1.1 Risks Associated with Obinutuzumab

As of 12 July 2017, 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 progressive multifocal leukoencephalopathy 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 4.3.2.1 and Appendix 7.

Hypersensitivity reactions with immediate (e.g., anaphylaxis) and delayed (e.g., serum sickness) onset have been reported in patients treated with obinutuzumab. Hypersensitivity reactions typically occur after previous exposure and very rarely with the first infusion. In 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 4.3.2.6 (see Table 6). Additional guidelines for management of TLS in this study are provided in Section 5.1.5 (see Table 12).

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 the treatment of neutropenia per institutional guidelines 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 4.3.2.6.

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 patients with CLL exposed to obinutuzumab, fatal hemorrhagic events have also been reported in Cycle 1. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients receiving concomitant

medication that could possibly worsen thrombocytopenia related events (e.g., platelet inhibitors and anticoagulants) may be at a 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 FL studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen in maintenance.

Reactivation of hepatitis B 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 progressive multifocal leukoencephalopathy has been reported in patients treated with obinutuzumab. The diagnosis of progressive multifocal leukoencephalopathy should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of progressive multifocal leukoencephalopathy 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 progressive multifocal leukoencephalopathy 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 progressive multifocal leukoencephalopathy in this study are provided in Section 5.1.5.

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 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.

5.1.3 Risks Associated with Lenalidomide

5.1.3.1 Embryo-Fetal Toxicity

Lenalidomide, a thalidomide analogue, is structurally related to thalidomide, a known human teratogenic active substance that causes severe life-threatening birth defects. In a developmental study in monkeys, lenalidomide caused limb abnormalities similar to birth defects caused by thalidomide in humans. If taken during pregnancy, lenalidomide is expected to have a teratogenic effect in humans.

Lenalidomide must not be taken by patients who are pregnant. In every country where lenalidomide has been approved, a risk minimization plan, which includes a pregnancy prevention program, is in place. Investigators must ensure that all specific local requirements that are applicable to the safe and effective use of lenalidomide are fulfilled prior to administration to patients. The risk minimization plan should be followed by prescribers and by patients using lenalidomide. In addition, because lenalidomide will be administered in combination with atezolizumab and obinutuzumab, patients must comply with contraceptive measures designed to ensure safe administration of all three

study treatments, as outlined in Section 4.1.1. Pregnancy testing and counseling should be performed if a patient misses her period or has unusual menstrual bleeding. Treatment with lenalidomide must be discontinued until it is confirmed that the patient is not pregnant.

5.1.3.2 Hematologic Toxicity

Lenalidomide can cause significant neutropenia and thrombocytopenia. Patients should have their CBCs monitored weekly for the first 8 weeks and at least monthly thereafter.

5.1.3.3 Venous and Arterial Thromboembolism

Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients treated with lenalidomide. Prophylactic anti-thrombotic medicines are recommended, especially in patients with additional thrombotic risk factors. The decision to take prophylactic measures should be made after a careful assessment of a patient's underlying risk factors. Thromboprophylaxis is presented in Section 4.3.2.6.

Patients with known risk factors for TE, including prior thrombosis, should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis (such as hormone replacement therapy), should be used with caution. A hemoglobin concentration of $>$12 g/dL should lead to discontinuation of erythropoietic agents.

Patients and physicians are advised to be observant of the signs and symptoms of TE. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

5.1.3.4 Tumor Flare Reaction

Tumor flare reaction (TFR) has occurred during investigational use of lenalidomide for treatment of CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain, and rash. Monitoring and evaluation for TFR is recommended in patients taking lenalidomide. TFR may mimic disease progression. Guidelines for the management of TFR are presented in Table 11.

5.1.3.5 Severe Skin Reactions

Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported during treatment with lenalidomide. These events can be fatal. Guidelines for the management of severe skin reactions are presented in Table 11. Patients with a history of erythema multiforme, Grade $\geq$3 rash, or blistering following prior treatment with immunomodulatory derivatives (such as thalidomide and lenalidomide) will not be enrolled in the study.

5.1.3.6 Tumor Lysis Syndrome

Fatal instances of TLS have been reported during treatment with lenalidomide. Patients at risk for TLS are those with high tumor burden prior to treatment. These patients should be monitored closely, and appropriate precautions should be taken.

5.1.3.7 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. The mechanism of drug-induced hepatotoxicity is unknown. Preexisting viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Liver enzymes are to be monitored periodically. Guidelines for the management of hepatotoxicity are presented in Table 11.

5.1.3.8 Renal Impairment

Lenalidomide is substantially excreted by the kidney. Patients with renal impairment (i.e., calculated creatinine clearance $<$60 mL/min) will not be enrolled in this study. Renal function will be monitored during the study, and the lenalidomide dose may be adjusted as outlined in Section 5.1.5 (see Table 11).

5.1.3.9 Thyroid Disorders

Cases of hypothyroidism and cases of hyperthyroidism have been reported during treatment with lenalidomide. Optimal control of comorbid conditions influencing thyroid function is recommended before initiating lenalidomide treatment. Baseline and ongoing monitoring of thyroid function is recommended.

5.1.3.10 Peripheral Neuropathy

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with long-term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

5.1.3.11 Second Primary Malignancies

Patients with multiple myeloma treated with lenalidomide in studies that included melphalan and SCT had a higher incidence of second primary malignancies (SPM), particularly acute myelogenous leukemia and Hodgkin's lymphoma. Patients are to be monitored for the development of second malignancies. A regular reminder will be sent to study investigators every 6 months in order to collect any new cases of SPMs.

5.1.3.12 Drug-Drug Interactions

Patients who are receiving digoxin should undergo periodic monitoring of digoxin plasma levels, due to increased maximum concentration observed and AUC with concomitant lenalidomide therapy

Co-administration of multiple dose lenalidomide (10 mg) with single dose warfarin (25 mg) had no effect on the pharmacokinetics of lenalidomide or warfarin. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide

administration. However, a close monitoring of PT and INR is recommended in patients receiving warfarin.

5.1.4 Risk of Overlapping Toxicities and Drug-Drug Interactions

The anticipated toxicities from the combined administration of atezolizumab with obinutuzumab and lenalidomide are expected to be manageable in the clinical setting. Hematologic toxicity (mainly neutropenia) is the most common toxicity associated with G-Len. Of interest, the risk of overlapping hematologic toxicity with the addition of atezolizumab to G-Len appears very low. Considering the risk associated with each individual component of the combination (Sections 5.1.1, 5.1.2, and 5.1.3) the expected overlapping non-hematologic toxicities summarized in Table 8 are IRRs, infections, cutaneous toxicity, GI toxicity, and elevated liver transaminases. Additionally, hypothyroidism is a toxicity associated with both atezolizumab and lenalidomide, reported in 4% of patients treated with atezolizumab (mild to moderate in severity) and with unknown frequency in lymphoma patients treated with lenalidomide. In one study of lenalidomide single agent in patients with myelodysplastic syndromes, hypothyroidism was reported in 6.8% of patients (Revlimid® U.S. Package Insert).

Lenalidomide is primarily excreted in the urine. Lenalidomide is not a substrate, inhibitor, or inducer of cytochrome P450 (CYP) group of enzymes (Kumar et al. 2009). Obinutuzumab and atezolizumab do not interact directly with CYP isoforms or other drug metabolizing enzymes or drug transporters. Cytokine modulation may be considered as an indirect mechanism through which a monoclonal antibody could alter CYP expression, but would only be relevant for drugs that are significantly metabolized via CYP enzymes. Therefore, clinically relevant PK DDIs are unlikely to occur between lenalidomide, obinutuzumab, and atezolizumab.

Table 8 Summary of Potentially Overlapping Adverse Events

Event		Atezolizumab [a]	Obinutuzumab [b,c]	Lenalidomide[d]	G-Len [e]
Hematologic Toxicity					
Neutropenia, Grade 3 or 4		0	5%–14%	33%–43%	26.1%
Febrile neutropenia		0	25%	2%–7%	3.4%
Thrombocytopenia, Grade 3 or 4		0	5%–8%	20% – 30%	10.2%
Anemia, Grade 3 or 4		4.6%	3%	6%–12%	1.1%
Non-Hematologic Toxicity					
IRRs	All grades	1.2%	73%–75%	0	14.8%
	Grade 3 or 4	0	11%	0	0
Infections	All grades	0	5%–41%	10%–27%[g]	25.0%
	Grade 3 or 4	0	10%	8%–10%	3.4%
Rash	All grades	13%	7%	18%–27%	12.5%
	Grade 3 or 4	0	0	1%–4%	0
Diarrhea	All grades	22.4% [f]	5%–8%	25%–31%	14.8%
	Grade 3 or 4	0	0	2%–6%	0
Vomiting	All grades	19.7%	5%	12%	2.3%
	Grade 3 or 4	0.2%	0	0	0
Nausea	All grades	27.8%	5%–9%	18%–30%	13.6%
	Grade 3 or 4	0.2%	0	2%	0
SGOT/SGPT increase	Grade 3 or 4	1.7% [f]	3%	2%	1.1%

IRR = infusion-related reaction.

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

[b] BO21003 Clinical Study Report (No. 1056428).

[c] BO20999 Clinical Study Report (No. 1036614) (high dose, NHL cohorts).

[d] Goy et al. 2013, Wiernik et al. 2008, Witzig et al, 2011, and Zinzani et al. 2013.

[e] Data from relapsed/refractory FL cohort from (Study MO28005 [GALEN]), events related to any study drug during the induction phase of treatment.

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

[g] Pneumonia was the most common Grade 3 or 4 infection.

5.1.5 Management of Specific Adverse Events

Study treatment may be delayed for toxicity for a maximum amount of time, as specified in the tables below. If study treatment is delayed for longer than the specified maximum, study treatment will be permanently discontinued. Treatment delays apply to all toxicities described below; dose modifications apply only to toxicities that are considered

to be related to lenalidomide. There will be no dose reductions of obinutuzumab or atezolizumab.

The lenalidomide dose may be reduced in 5-mg increments one or two times, depending on the starting dose, as outlined in Table 9. There will be no more than one dose reduction per treatment cycle. If the lenalidomide dose is reduced, re-escalation is not permitted.

Table 9 Lenalidomide Dose Reduction

Starting Dose	First Reduction	Second Reduction
20 mg	15 mg	10 mg
15 mg	10 mg	5 mg
10 mg	5 mg	—

If a lenalidomide-related toxicity occurs during lenalidomide treatment (i.e., before Day 21 of the cycle), lenalidomide must be withheld until criteria for recovery have been met (i.e., improves to Grade $\leq$ 2 or baseline values).

If recovery is observed prior or on Day 15 of the cycle, lenalidomide may be resumed at the same dose for the remainder of the cycle (through Day 21; missed doses will not be made up) at the discretion of the investigator. If the investigator considers that resuming lenalidomide at the same dose within the cycle represents an unacceptable risk for the patient, lenalidomide shall be resumed at reduced dose or withheld for the remainder of the cycle. For subsequent cycles, lenalidomide will be resumed at reduced doses.

If recovery is observed after Day 15 of the cycle, lenalidomide will not be resumed for the current cycle. For subsequent cycles, lenalidomide will be resumed at reduced doses.

Guidelines for management of toxicities during induction are provided in Section 5.1.5.2. Guidelines for management of toxicities during maintenance are provided in Section 5.1.5.3.

5.1.5.1 Systemic Immune Activation

Recommendations regarding early identification and management of systemic immune activation are provided below. In the event of suspected systemic immune activation, atezolizumab should be withheld, and the Medical Monitor should be contacted immediately for additional guidance.

Early disease recognition is critical, and systemic immune activation should be suspected if, in the absence of an alternative etiology, the patient meets two or more of the following criteria:

- Hypotension that is refractory to aggressive IV fluid challenge

  Vasopressor support may be required.
- Respiratory distress that requires aggressive supportive care

  Supplemental oxygen and intubation may be required.
- Fever $>38.5°C$
- Acute renal or hepatic failure
- Bleeding from coagulopathy
- Any of the following unexplained laboratory abnormalities (change from baseline): cytopenias (in two or more lineages), significant transaminitis, and coagulopathy

For patients with suspected systemic immune activation, an 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)

Laboratory tests with normal results should be repeated frequently in patients for whom a high clinical suspicion of systemic immune activation exists.

If cytopenias are present (Grade ≥ 2 in two or more lineages) or ferritin is $\geq$ 3000 ng/mL, the following evaluations should also be performed:

- Bone marrow biopsy and aspirate (assess for evidence of hemophagocytosis)
- Soluble interleukin 2 (IL-2) receptor (sCD25)
- Natural killer cell activity
- Cytomegalovirus, Epstein-Barr virus, and herpes-simplex virus evaluation (for reactivated or active disease)

Diagnostic criteria and recommended management for systemic immune activation are provided in Table 10. The diagnostic criteria apply only when alternative etiologies have been excluded.

Table 10 Diagnostic Criteria and Management for Systemic Immune Activation

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

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken
≥ 4 major criteria	Consistent with systemic immune activation	• Permanently discontinue atezolizumab. • Consider treatment with an immunosuppressive agent (i.e., tocilizumab, infliximab, cyclosporine A, or etoposide) and IV corticosteroids (i.e., methylprednisolone 1 g once daily or equivalent). • Contact the Medical Monitor for additional recommendations. • Consider HLH-94 protocol if there is no clinical improvement.
3 major criteria OR 2 major plus ≥ 3 minor criteria	Probable systemic immune activation	• Depending on clinical severity, follow guidelines for "Consistent with systemic immune activation" or "Possible systemic immune activation" diagnosis. • The Medical Monitor may be contacted for recommendations.

Table 10 Diagnostic Criteria and Management for Systemic Immune Activation (cont.)

Diagnosis and Management of Systemic Immune Activation		
Number of Criteria	Diagnosis	Action to Be Taken
2 major plus ≤ 2 minor criteria OR 1 major plus ≥ 4 minor criteria	Possible systemic immune activation	• Withhold atezolizumab. • Consider treatment with IV corticosteroids. • The Medical Monitor may be contacted for additional recommendations. • Follow guidelines for "Consistent with systemic immune activation" diagnosis if there is no clinical improvement or if clinical worsening occurs. • If clinical improvement occurs, atezolizumab may be resumed following a benefit-risk assessment by the Medical Monitor.
ALT = alanine transaminase; AST = aspartate transaminase; GGT = γ-glutamyl transpeptidase; IL-2 = interleukin-2; IV = intravenous; LDH = lactate dehydrogenase; LFT = liver function test. Notes: Criteria are adapted from a Delphi Survey of 26 experts who provided helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients (Hejblum et al. 2014). Case reports and recommendations have been published for cytokine-release syndrome (Teachey et al. 2013; Lee et al. 2014; Maude et al. 2014), and, on the basis of etiologic similarities, these practices have been incorporated into the above treatment recommendations. These recommendations do not replace clinical judgment and are intended as suggested guidance.		

An adverse event of systemic immune activation should be reported on the Adverse Event eCRF if it meets the criteria for "consistent with systemic immune activation" or "probable systemic immune activation" as outlined above in Table 10.

5.1.5.2 Toxicities during Induction Treatment

Hematologic Toxicities during Induction Treatment

Table 11 provides guidelines for management of hematologic toxicities that occur during induction treatment. Hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia. Lymphopenia is not considered a hematologic toxicity but rather an expected outcome of therapy.

Table 11 Guidelines for Management of Hematologic Toxicities that Occur during Induction Treatment

Event	Action To Be Taken
Grade 3 or 4 hematologic toxicity [a,b]	**For patients on any dose of lenalidomide:** • 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. **For patients on a lenalidomide dose ≥10 mg who have had one or no prior lenalidomide dose reductions** • Withhold study treatment (except atezolizumab).[c] • Administer RBCs or platelets as required. • If patient has not already initiated G-CSF, initiate prophylactic G-CSF for current and subsequent cycles. • For patients receiving primary thromboprophylaxis who develop platelet count of <20,000/μL, reduce the dose of LMWH or consider temporarily withholding platelet inhibitors, as applicable. If patient's condition doesn't allow interruption of the anticoagulant/antiaggregant treatment, adequate platelet transfusion support and close monitoring of the hematologic and coagulation functions are required. • For lenalidomide dose reductions, refer to guidelines presented in Section 5.1.5. • If the event is ongoing on Day 1 of the next cycle but improves to Grade ≤2 or baseline ≤14 days after the scheduled date of the cycle, resume obinutuzumab at full dose and resume lenalidomide at current dose or reduced dose if the patient received <21 days of lenalidomide due to toxicity (see Section 5.1.5). • If the event is ongoing on Day 1 of the next cycle but improves to Grade ≤2 or baseline 15–21 days after the scheduled date for the next cycle, resume obinutuzumab at full dose and resume lenalidomide at a reduced dose [a,b] per guidelines in Section 5.1.5[a,b] for current and subsequent cycles. • If study treatment is withheld for >21 days, permanently discontinue lenalidomide. Obinutuzumab may be continued for patients experiencing clinical benefit as determined by the investigator after discussion with the Medical Monitor. • Permanently discontinue study treatment if any of the following events occur: Grade 3 or 4 thrombocytopenia that results in significant bleeding per investigator judgment Recurrent Grade 3 or 4 neutropenia associated with fever >38°C lasting >5 days or documented infection despite use of G-CSF and after one lenalidomide dose reduction Recurrent Grade 4 neutropenia or thrombocytopenia lasting >7 days despite use of G-CSF (for neutropenia) and after one lenalidomide dose reduction **For patients on a lenalidomide dose of 5 mg and patients who have had two prior lenalidomide dose reductions:** • Permanently discontinue lenalidomide. Obinutuzumab may be continued for patients experiencing clinical benefit as determined by the investigator after discussion with the Medical Monitor.

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

[a] Dose modifications apply only to events that are considered to be related to lenalidomide.

[b] If cytopenia is thought to be caused mainly by non–Hodgkin's lymphoma infiltration of the bone marrow, the investigator may decide not to reduce the dose of lenalidomide.

[c] For Grade 3 neutropenia, only if sustained (≥ 7 days) Grade 3 or ≥ Grade 3 associated with fever (temperature ≥ 38.5°C).

Non-Hematologic Toxicities during Induction Treatment

Table 12 provides guidelines for management of non-hematologic toxicities that occur during induction treatment.

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

Table 12 Guidelines for Management of Non-Hematologic Toxicities

Event	Action To Be Taken
General guidance for treatment delays and discontinuation	• If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses of obinutuzumab will not be skipped but given after resolution of toxicity. • When a treatment cycle is delayed because of a toxicity resulting from any component of the regimen, all study treatment should generally be held and resumed together to remain synchronized. • If it is anticipated that atezolizumab will be delayed by >21 days, obinutuzumab and lenalidomide should be given without atezolizumab if there is no contraindication. • If one drug is discontinued, treatment with the other two drugs may be continued for patients experiencing clinical benefit as determined by the investigator after discussion with the Medical Monitor. • Permanently discontinue study treatment if any of the following events occur: – Grade ≥3 non–immune-related adverse event that is considered to be related to study treatment and does not resolve to Grade ≤2 within 21 days – Non–immune-related adverse event that is considered to be treatment related and requires study treatment to be withheld for >21 days – Immune-related adverse event that requires atezolizumab to be withheld for >42 days, unless approved by the Medical Monitor
IRRs and anaphylaxis	• Guidelines for management of IRRs are provided in Sections 4.3.2.1 (obinutuzumab) and 4.3.2.2 (atezolizumab). • 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 5.1.5.1
Renal toxicity	• Adjust the dose of lenalidomide [a] as outlined below: – If creatinine clearance is ≥30 but <60 mL/min, lenalidomide should be given at a dose of 10 mg/day. – If creatinine clearance is <30 mL/min and dialysis is not required, lenalidomide should be given at a dose of 10 mg every other day. – If creatinine clearance is <30 mL/min and dialysis is required, lenalidomide should be given at a dose of 5 mg/day. On dialysis days, the dose should be administered after dialysis.

Table 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
TLS	Clinical TLS [b]	• Withhold study treatment. • Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. Rasburicase therapy (if approved by the local health authority) may be administered as needed to reduce hyperuricemia. • If symptoms resolve completely, resume atezolizumab and obinutuzumab at full dose and resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.5 for current and subsequent cycles. • Perform chemistry panel every other day for the first week after re-initiation of lenalidomide.
	Laboratory TLS [b]	• Withhold study treatment. • Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care as clinically indicated. • If laboratory abnormalities have resolved completely, resume atezolizumab and obinutuzumab at full dose and resume lenalidomide either at current dose or at a reduced dose [a] per guidelines in Section 5.1.5 for current and subsequent cycle, at the investigator's discretion.
Peripheral neuropathy	Grade 4 or Myasthenia gravis (any grade) or Guillain-Barre (any grade)	• Permanently discontinue study treatment.
	Grade 2 or 3	• Withhold study treatment and evaluate patient at least every 7 days. • If neurotoxicity is considered likely related to lenalidomide and there is improvement to Grade $\leq$ 1 or baseline, resume atezolizumab and obinutuzumab at full dose and resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.5 for current and subsequent cycles. • Permanently discontinue atezolizumab for life-threatening immune-related neuropathy.
New-onset neurologic manifestations suggestive of progressive multifocal leukoencephalopathy		• Withhold study treatment. [a] • Consult with a neurologist if progressive multifocal leukoencephalopathy is suspected (refer to Section 5.1.1.5 for guidance on investigations). • If progressive multifocal leukoencephalopathy is ruled out, resume atezolizumab and obinutuzumab at full dose and resume lenalidomide at current dose. • If progressive multifocal leukoencephalopathy is confirmed, permanently discontinue study treatment.

Table 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
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 at full dose and lenalidomide at current dose. – taper corticosteroids over 1 month. Contact Medical Monitor before resuming atezolizumab.
Immune-related nephritis	*Grade 3 or 4*	• *Permanently discontinue study treatment.* • *Refer patient to renal specialist.* • *Consider renal biopsy and supportive measures.* • *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.*[d] *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.* [e] • *If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.* [f]
	Grade 1	• *Continue study treatment.* • *Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.*

Table 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

AST, ALT, or bilirubin increase	Grade ≥ 3 (or ≥ 10 × ULN for patients with liver involvement)	• Withhold study treatment 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 may be resumed at full dose and lenalidomide 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 and atezolizumab at full dose and resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.5 for current and subsequent cycles. • Permanently discontinue atezolizumab 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 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Amylase or lipase increase +/- abdominal pain	Grade ≥ 3	• Withhold study treatment. • Investigate etiology. Consult with a gastroenterologist if immune etiology is suspected. • For isolated increase of lipase or amylase that is asymptomatic and considered related to atezolizumab, obinutuzumab/rituximab and lenalidomide 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 there is improvement to Grade ≤ 2 and patient is asymptomatic, resume obinutuzumab at full dose and resume lenalidomide at current dose. Atezolizumab may be resumed at full dose after approval 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 life-threatening pancreatitis or recurrent Grade 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. • 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 there is improvement to Grade ≤ 1, resume obinutuzumab at full dose and resume lenalidomide at current dose • Permanently discontinue atezolizumab.
	Grade 1 or 2	• Consult with an ophthalmologist. • Treat with topical corticosteroid eye drops. If symptoms persist, topical immunosuppressive therapy may also be considered. • Discontinue atezolizumab if symptoms persist.

Table 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Diarrhea/Colitis	Grade 4	• Permanently discontinue study treatment. • Investigate etiology. Consult with a gastroenterologist (refer to Atezolizumab Investigator's Brochure for guidance 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. • Investigate etiology. Consult with a gastroenterologist if immune etiology is suspected (refer to Section 5.1.5.1 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 ≤1, resume obinutuzumab at full dose and resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.5. In case of immune-related event, atezolizumab may be resumed at full dose if colitis has cleared as confirmed by sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy. 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 ≤10 mg/day of prednisone or equivalent.

Table 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Pneumopathy, non-infectious (i.e., dyspnea, hypoxia, pulmonary infiltrates)	Grade 3 or 4	• Permanently discontinue atezolizumab. Withhold obinutuzumab and lenalidomide. • Investigate etiology. Consult with a pulmonologist if immune etiology is suspected (refer to Atezolizumab Investigator's Brochure for guidance). • Treat immune-related pneumopathy with corticosteroids following guidance provided in the Atezolizumab Investigator's Brochure. • If symptoms have resolved and CT lung findings are clear, resume obinutuzumab at full dose and resume lenalidomide at current dose.
	Grade 2	• Withhold atezolizumab for immune-related pneumopathy. • Treat with corticosteroids following guidance provided in the atezolizumab Investigator's Brochure. • If there is improvement to Grade ≤ 1, resume atezolizumab after corticosteroids have been tapered to ≤ 10 mg/day of oral prednisone or equivalent. Discuss with Medical Monitor before resuming atezolizumab. • Treat as Grade 3– 4 if recurrent episode of immune pneumopathy.
Tumor flare reaction	Grade 3–4 [c]	• Withhold study treatment. • Administer corticosteroids, NSAIDs, and/or narcotic analgesics at investigator's discretion. • If there is improvement to Grade ≤ 1, resume obinutuzumab and atezolizumab at full dose and resume lenalidomide at a reduced dose per guidelines in Section 5.1.5 for current and subsequent cycles.
	Grade 1–2 [c]	• Continue study treatment. • Administer corticosteroids, NSAIDs, and/or narcotic analgesics at investigator's discretion.

Table 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Dermatologic toxicity: Grade ≥2	Grade 3 with blistering or Grade 4	• Permanently discontinue study treatment.
	Grade 2 or Grade 3 without blistering	First occurrence: • Withhold study treatment and evaluate patient at least every 7 days. • Investigate etiology. Consult with a dermatologist. • Topical corticosteroids may be required. • If immune etiology is suspected, consider oral prednisone 10 mg or equivalent. If event is unresolved after 48 – 72 hours, administer oral prednisone 60 mg or equivalent. • If there is improvement to Grade ≤1, resume obinutuzumab at full dose and resume lenalidomide at a reduced dose [a] per guidelines in Section 5.1.5 for current and subsequent cycles. Atezolizumab may be resumed at full dose if the event is resolved and systemic corticosteroids dose is ≤ 10 mg/day of oral prednisone or equivalent. Contact Medical Monitor before resuming atezolizumab. Second occurrence: • Permanently discontinue study treatment.
Hypothyroidism		• Investigate etiology. Consult with an endocrinologist (refer to the Atezolizumab Investigator's Brochure for guidance if immune etiology is suspected). • Start thyroid replacement hormone. • Monitor TSH weekly. Asymptomatic elevation of TSH • Continue study treatment. Symptomatic elevation of TSH • Withhold study treatment. • If symptoms are controlled and TSH levels are decreasing, resume obinutuzumab and atezolizumab at full dose and lenalidomide at current dose. • Permanently discontinue atezolizumab for Grade ≥ 3 hypothyroidism.

Table 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Hyperthyroidism		For asymptomatic patients with TSH < 0.5 mU/L: • Perform TSH, free T4, and T3 tests every 4 weeks. For asymptomatic patients with TSH < 0.1 mU/L or symptomatic patients • Withhold study treatment. • 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.
Hypophysitis (pan-hypopituitarism)	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 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
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 IV 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 Medical Monitor before resuming atezolizumab.
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.

Table 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Immune-related myocarditis, cont.	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.
Venous thrombosis or embolism		• Withhold lenalidomide. • Start anticoagulation treatment. • After patient has been stabilized on anticoagulants and any complications of the thromboembolic event have been managed, lenalidomide may be resumed at current dose at investigator's discretion, dependent upon a benefit-risk assessment. Anticoagulants should be continued during the course of lenalidomide treatment.
Other non-hematologic toxicities (i.e., not described above), excluding alopecia, nausea, and vomiting	Grade 3 or 4	Grade 4 events • Permanently discontinue study treatment. Grade 3 events • Withhold study treatment. • If there is improvement to Grade ≤ 1 or baseline, resume obinutuzumab and atezolizumab at full dose and, if the event is considered related to lenalidomide, resume lenalidomide at a reduced dose per guidelines in Section 5.1.5 for current and subsequent cycles; if the event is not related to lenalidomide, resume lenalidomide at current dose. • For Grade 3 laboratory abnormalities that are isolated, asymptomatic and considered not clinically significant, study treatment may be either continued or delayed and resumed at the current dose, upon improvement to at least Grade 2 at the investigator's discretion and in agreement with the Medical Monitor.

Table 12 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action To Be Taken
Other non-hematologic toxicities, cont.	Grade 2	• Withhold study treatment. • If there is improvement to Grade ≤ 1 or baseline, resume obinutuzumab and atezolizumab at full dose and resume lenalidomide at current dose. • For Grade 2 laboratory abnormalities that are isolated, asymptomatic and considered not clinically significant treatment may be continued at the current dose at the investigator's discretion.

CT = computed tomography; FL = follicular lymphoma; G-CSF = granulocyte colony-stimulating factor; IRR = infusion-related reaction; IV = intravenous; LMWH = low-molecular-weight heparin; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NHL = non-Hodgkin's lymphoma; NSAID = nonsteroidal anti-inflammatory drug; TLS = tumor lysis syndrome; TSH = thyroid-stimulating hormone; ULN = upper limit normal.

[a] Dose modifications apply only to events that are considered to be related to lenalidomide.

[b] According to Cairo-Bishop classification system.

[c] Graded according to NCI CTCAE Version 3.0.

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

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

[f] *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.*

5.1.5.3 Toxicities during Maintenance Treatment

Table 13 provides guidelines for management of toxicities that occur during maintenance treatment.

Table 13 Guidelines for Management of Toxicities That Occur during 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. • Withhold obinutuzumab and lenalidomide. • Administer G-CSF for neutropenia per institutional guidelines. • Administer RBCs or platelets as required. • If there is improvement to Grade ≤2, resume obinutuzumab and lenalidomide at same dose. • If study treatment 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 12 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. • If there is 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.

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 5.3.6.10
- 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 in-patient hospitalization (see Section 5.3.6.11)
- 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 v3.0; see Section 5.3.4); 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).

SPMs should be also reported as Serious Adverse Events. This requirement includes any SPM, regardless of causal relationship to study treatment occurring at any time during the study, from the time of signing the informed consent form up to 3 years after the last dose of lenalidomide.

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

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

- 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 5.3.6.7)
- 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.
- 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 progressive multifocal leukoencephalopathy
- 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

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 5.3.4), and causality (see Section 5.3.5).

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 35 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 study treatment; and for SPMs (related and unrelated), which should be reported as serious adverse events until up to 3 years after the last dose of lenalidomide.

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 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

During the DLT assessment window (Cycle 2), adverse events identified as DLTs, as defined in Section 3.1.2.1, are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.3.3 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?"

5.3.4 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity, with the exception of TFRs that will be graded using NCI CTCAE v3.0. Table 14 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 14 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.

5.3.5 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.

5.3.6 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.

5.3.6.1 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.

5.3.6.2 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.

5.3.6.3 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.

5.3.6.4 Persistent or Recurrent Adverse Events

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

5.3.6.5 Abnormal Laboratory Values

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

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.6.4 for details on recording persistent adverse events).

5.3.6.6 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 5.3.6.4 for details on recording persistent adverse events).

5.3.6.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.6.2) 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).

5.3.6.8 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.

5.3.6.9 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").

5.3.6.10 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 3). 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.

5.3.6.11 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

5.3.6.12 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)
- Adverse events identified as DLTs
- 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.*

Telephone No.: [redacted]

Mobile Telephone No.:

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only 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 35 days after the last dose of study treatment. DLTs will be reported during the DLT assessment window. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the 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 or within 18 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. 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. The patient should be referred to an obstetrician or gynecologist, preferably one who is experienced in reproductive toxicity, for further evaluation and counseling. The patient shall be instructed to return any unused portion of the study drug to the Investigator.

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 Exposure of Pregnant Female to Lenalidomide

If a pregnant female not enrolled in the study (e.g., caregiver or pharmacist) is exposed to lenalidomide, the Adverse Event 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 exposure), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. The woman should be referred to an obstetrician or gynecologist, preferably one who is experienced in reproductive toxicity, for further evaluation and counseling.

5.4.3.4 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).

5.4.3.5 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 35 days after the last dose of study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

An exception is made for Grade 3–4 infections (related and unrelated to study treatment), which should be reported until up to 2 years after the last dose of study treatment. In addition, SPMs (related and unrelated to study treatment) should be reported as serious adverse events until up to 3 years after the last dose of lenalidomide.

The Sponsor should also be notified of events of second malignancies indefinitely (even if the G+Atezo+len 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
- Lenalidomide *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 dose-escalation phase followed by an expansion phase. The dose-escalation phase is designed to determine the RP2D for lenalidomide when combined with fixed doses of obinutuzumab and atezolizumab. During the expansion

phase, patients will undergo treatment with lenalidomide at the RP2D, obinutuzumab, and atezolizumab.

6.1 DETERMINATION OF SAMPLE SIZE

Limited dose finding will be conducted during the dose-escalation phase of this study. The estimated sample size follows from the dose-escalation rules for a 3+3 algorithm, as outlined in Section 3.1. It is anticipated that enrollment of two dosing groups of 3–6 patients each, for a total of 6–12 patients with relapsed or refractory FL, will be required to establish the RP2D during the dose-escalation phase.

Approximately 40 patients will be enrolled during the expansion phase.

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 from the GALEN study (Morschhauser et al. 2017) indicate that the historical CR rate based on PET-CT scans is approximately 40% in relapsed or refractory setting, 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 $<$ 46%, assuming an observed PET-CT–defined CR rate of 60%. Updated estimates of the proportion of patients expected to achieve a PET-CT–defined CR are expected to be available from ongoing studies by the time of the first interim analysis and will be used as reference data.

Table 15 lists the two-sided 90% Clopper-Pearson exact CI for the true probability of achieving a PET-CT–defined CR at the EOI for a range of observed proportions based on a sample of 40 patients.

Table 15 Potential 90% CI for the True Probability of Achieving a PET-CT–Defined Complete Response at EOI

Observed Proportion of Patients Achieving a PET-CT–Defined CR at EOI (n = 40)	Two-Sided 90% Clopper-Pearson CI [a] for True Population PET-CT–Defined CR (n = 40)
0.32	(0.20, 0.46)
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)

CI = confidence interval; 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 DEFINITION OF ANALYSIS POPULATIONS

The following populations are defined:

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

6.3 SUMMARIES OF CONDUCT OF STUDY

Enrollment, 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 as well as any dose modifications will be listed. The number of doses, treatment cycles, average dose received, for each treatment component will be summarized using descriptive statistics (mean, standard deviation, median, and range).

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics, such as age, sex, race, and duration of malignancy, will be summarized using descriptive statistics (mean, standard deviation, median, and range) for continuous variables and frequencies and percentages for categorical variables.

6.5 SAFETY ANALYSES

The safety analysis will be performed on the primary population; additional safety analysis will be performed on the ITT population.

The safety analyses will be performed separately for each study phase (i.e., dose escalation and expansion).

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 the first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 grade. All serious adverse events, adverse events of special interest, and selected events 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 data will be displayed by time, with Grade 3 and 4 values identified as appropriate.

6.6 EFFICACY ANALYSES

6.6.1 Primary Efficacy Endpoint

The efficacy analysis will be performed on the primary population. Additional efficacy analysis will be performed on the ITT population.

Patients who received lenalidomide at the RP2D during the dose-escalation phase will be pooled with patients treated in the expansion phase.

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 (see Appendix 3). Point estimates will be presented, along with the corresponding two-sided 90% Clopper-Pearson exact CIs. Patients without an EOI tumor assessment will be considered non-responders.

6.6.2 Secondary Efficacy Endpoints

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

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

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

For all secondary efficacy endpoints, 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-CRs and non-responders, respectively.

6.6.3 Exploratory Efficacy Endpoints

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

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

PFS, EFS, DFS, DOR, and overall survival (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 EFS and PFS analysis, data for patients without post-baseline tumor assessments will be censored at the date of initiation of study treatment plus 1. For the DFS analysis, data for patients without post-first CR tumor assessments will be censored at the date of first CR tumor assessments + 1 day. OS analyses, 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, 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.

6.7 PHARMACOKINETIC ANALYSES

Plasma/serum concentrations of obinutuzumab, atezolizumab, and lenalidomide will be tabulated, summarized, and plotted after appropriate grouping. As appropriate, PK parameters (e.g., AUC, time to maximum concentration, maximum concentration, and half-life) may also be calculated, tabulated, and summarized after appropriate grouping. Additional PK and PK/PD analyses (e.g., population modelling, including pooled analyses across studies) may also be performed as appropriate. If done, these additional analyses may be reported separately from the Clinical Study Report. At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of lenalidomide.

6.8 IMMUNOGENICITY ANALYSES

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

6.9 BIOMARKER ANALYSES

Exploratory analyses of biomarkers related to tumor biology and study treatment mechanisms of action will be conducted. Analyses will assess the prognostic and/or predictive value of candidate biomarkers with respect to 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.

6.10 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 treated at the RP2D of lenalidomide have been evaluated for PET-CT–defined CR at the EOI. Additional analyses will be conducted every 4 months to guide early stopping of enrollment for safety on the basis of observed toxicities. Stopping rules for excess toxicity, including fatal adverse events, have been included (see Section 6.11).

During the expansion phase, a modified version of the predictive probability design (Lee and Lui 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 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 is lower or higher than expected, the IMC will review the data and decide whether to recommend an early decision to stop enrollment. 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.

6.11 STOPPING RULES FOR SAFETY

In the event that any of the following criteria are met at any time in the course of the study, the IMC will be immediately convened to review and provide a recommendation for further conduct of the study:

- Fatal adverse events ≥ 10%
- Grade 3–4 adverse events ≥ 75%

The fatal adverse event threshold of 10% is derived from the completed GADOLIN study (Sehn et al. 2015) and the ongoing external study GALEN (Morschhauser et al. 2017), in which the occurrence rates of Grade 5 adverse events were 6% and 3.4%, respectively. Based on these two studies, the assumed historical control fatal adverse event rate is 5%, and with a 5% addition as a trigger for IMC review, a threshold rate of 10% is used for the stopping rules. The fatal adverse events will be continuously monitored during the conduct of the study and if the number of fatal adverse events reach the pre-specified threshold, the IMC will be immediately convened to decide whether to continue or stop the study (see Table 16). For each of these incidence rates, the minimized false positive probabilities and the true positive probability of correctly triggering an IMC safety review when the observed fatal adverse event rates are 5% higher than the historical control rate are presented.

Table 16 Early Stopping Rules Based on Number of Fatal Adverse Events

Interim look, n	# (rate, %) of fatal (Grade 5) AE(s) required for an IMC review	Probability of early stopping [a]	
		Probability of correct stop if true experimental regimen fatal AE rate =10% (historical control rate + 5%)	Probability of incorrect stop if true experimental regimen fatal AE rate =5%
27–30	2 (7%)	59%	19%
31–40	2 (5%)	78%	32%
41–45	3 (7%)	67%	19%

AE = adverse event; IMC = Internal Monitoring Committee.

Note: The assumed historical control fatal adverse event rate is 5%.

[a] Assessed for upper limit of the interim look sample size (i.e., for n=30, 40, 45).

In addition to fatal adverse events, Grade 3/4 adverse events, which represent severe non-fatal events, will be closely monitored. The threshold of 75% for Grade 3/4 adverse events is derived from the external study GALEN (Morschhauser et al. 2017) and the completed study GADOLIN (Sehn et al. 2015), where the occurrence rates of Grade 3/4 adverse events were 57% and 62%, respectively.

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 on the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for 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 (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting 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 the FDA and other 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.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

EDC will be used for this study. An IxRS will be used to assign patient numbers. A central laboratory will be used for a subset of laboratory assessments as specified in Section 4.5.7; otherwise, local laboratories will be used. A central independent review facility will be used to collect PET-CT and CT scans, and the IRC will perform independent assessments of response for all patients enrolled in the study (separate IRC charter will contain all details).

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

	Screening [a]		Induction (6 months; 28-day cycles)								EOI	Maint. (24 months)		EOM [b]		
	D −28 to D −1	D −14 to D −1	Cycle 1 (± 1 days)				Cycles 2–6 (± 2 days)				After Last Induction Dose [c]	Monthly (± 3 days)	Every 2 months (± 3 days)	35 days after Last Dose	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
			D1	D8	D15	D22	D1	D8	D15	D22		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 [nn]	x	x		
12-Lead ECG	x										x [g]			x		
Complete physical examination [h,i]	x		x													
Targeted physical examination [i,j]							D1, Cycles 2 and 4				x		x	x	x	
Ann Arbor, FLIPI, and FLIPI2	x															
B symptoms [k]	x															
β_2 microglobulin		x														
Hematology [l]		x	x [m,n]	x [n]	x [n]	x [n]	x [n]	x [n,o]	x [n]	x [n,o]	x [g]	x [n, nn]	x	x		
Chemistry panel (serum or plasma) [p]		x	x [m,n]	x [n]	x [n]	x [n]	x [n]	x [n,o]	x [n]	x [n,o]	x [g]	x [n, nn]	x	x		
Coagulation (INR, aPTT [or PTT], and PT)		x														

Appendix 1
Schedule of Assessments (cont.)

	Screening [a]		Induction (6 months; 28-day cycles)								EOI	Maint. (24 months)		EOM [b]		
	D −28 to D −1	D −14 to D −1	Cycle 1 (± 1 days)				Cycles 2–6 (± 2 days)				After Last Induction Dose [c]	Monthly (± 3 days)	Every 2 months (± 3 days)	35 days after Last Dose	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
			D1	D8	D15	D22	D1	D8	D15	D22		D1	D1			
Urinalysis (dipstick)		x	As clinically indicated													
Pregnancy test [q]		x [q]	x [q]	x [q]	x [q]	x [q]	x [q]									
Hepatitis B and C testing [r]	x															
TSH, T3, T4	x		Every 3 months													
Quantitative IgA, IgG, IgM			x								x	x [s]		x	x [t]	
HAHA sample for obinutuzumab			x [u]													
Anti-therapeutic antibody sample for atezolizumab			x [u]													
PK sample for obinutuzumab			x [u]													
PK sample for atezolizumab			x [u]													
PK sample for lenalidomide			x [u]													
Plasma for soluble PD-L1			x [n]													
Whole blood for MRD [v]			x [n,v]								x [v]	x [s,v]				
Whole blood for lymphocyte immunophenotyping [w]			x [n]				x [n]				x	x [s]		x	x [t]	
Whole blood for T-cell receptor repertoire in PBMCs			x [n]				x [n,o]				x	x [x]				

Appendix 1
Schedule of Assessments (cont.)

		Screening [a]		Induction (6 months; 28-day cycles)								EOI	Maint. (24 months)		EOM [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
		D −28 to D −1	D −14 to D −1	Cycle 1 (± 1 days)				Cycles 2–6 (± 2 days)				After Last Induction Dose [c]	Monthly	Every 2 months	35 days after Last Dose		
													(± 3 days)				
				D1	D8	D15	D22	D1	D8	D15	D22		D1	D1			
Plasma for soluble PD-L1				x [n]		x [n]		x [n,o]		x [n,o]							
Optional peripheral blood sample for RCR [y]				x [n]													
Tumor tissue specimen (leftover tissue may be used for optional RCR specimen [y])		x [z]						x [aa]				x [aa]					
Concomitant medications [bb]		x [bb]		To be recorded continually until end of treatment [bb]													
Adverse events [cc]		x		To be assessed continually [cc]													
PET-CT scan		x [dd]										x [ee]	x [ff]				
CT scan [gg]		x [gg]						x [hh]				x [ee]	x [hh]		x [ii]	x [jj]	
Bone marrow biopsy and aspirate		x [kk]										x [ee,ll]	x [ll]		x [ii,ll]		
Study treatment administration	Obinutuzumab [mm]			x	x	x		x						x			
	Atezolizumab [mm]							x		x			D1, D2				
	Lenalidomide [mm]			D1–21				D1–21					D1–21				

Appendix 1
Schedule of Assessments (cont.)

	Screening [a]		Induction (6 months; 28-day cycles)								EOI	Maint. (24 months)		EOM [b]		
	D −28 to D −1	D −14 to D −1	Cycle 1 (± 1 days)				Cycles 2–6 (± 2 days)				After Last Induction Dose [c]	Monthly	Every 2 months	35 days after Last Dose	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
												(± 3 days)				
			D1	D8	D15	D22	D1	D8	D15	D22		D1	D1			
New anti-lymphoma treatment															x	x
Survival follow-up																x

CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOI = end of induction; EOM = end of maintenance; FLIPI = Follicular Lymphoma International Prognostic Index; FU = follow-up; HAHA = human anti-human antibody; IgA = immunoglobulin A; IgG = immunoglobulin G; 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; SPM = second primary malignancies; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; wk = week.

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

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

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

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

[d] Patients who complete treatment or 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 be evaluated for survival status and new anti-lymphoma treatment every 3 months until the end of the study. The end of the study is defined as the time when all enrolled patients have completed or discontinued study treatment (including induction treatment and maintenance treatment as applicable).

[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. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For obinutuzumab infusions: For the first cycle 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, and unexplained weight loss >10% of body weight over 6 months.

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

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

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

[o] Cycles 2 and 3 only.

[p] 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.

[q] All women of childbearing potential will have two negative serum pregnancy test results prior to initiating treatment: at 10–14 days prior to Day 1 of Cycle 1 and within 24 hours prior to Day 1 of Cycle 1. Urine pregnancy tests are required after treatment initiation (including times of treatment interruption) as follows: every week during the first cycle and then every 4 weeks during treatment for women with regular menstrual cycles or every 2 weeks during treatment for women with irregular menstrual cycles, any time the patient misses her period or has unusual menstrual bleeding, at the time of treatment discontinuation, and at least 35 days after the last dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

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

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

[u] See Appendix 2 for detailed PK collection schedule.

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

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

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

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

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

[aa] 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.

[bb] Includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to the screening period until the EOI or EOM visit, whichever occurs later.

[cc] 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 35 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 study treatment; and for SPM (related and unrelated), which should be reported as serious adverse events until up to 3 years after the last dose of lenalidomide.The investigator should follow each adverse event until the event has resolved to baseline grade or better, until the event is assessed as stable by the investigator, until the patient is lost to follow-up, or until 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.

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

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

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

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

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

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

[jj] Perform every 6 months.

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

[ll] 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).

[mm] Refer to Sections 4.3.2.4 and 4.3.2.5 for details on dosing and schedule. At each cycle, each patient will be supplied with only enough lenalidomide for that cycle. During maintenance treatment, lenalidomide will be administered for a maximum of 12 months.

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

Appendix 2
Pharmacokinetic and Immunogenicity Sampling Schedule for Obinutuzumab, Atezolizumab, and Lenalidomide

Study Visit		Serum Obinutuzumab PK Sample [a,b,c]	Serum Atezolizumab PK Sample [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Atezolizumab Anti-Therapeutic Antibody Sample [a]	Plasma Lenalidomide PK Sample [a,d]
Induction during Dose Escalation and Expansion (Cycles 1–6; 28-day cycles)						
Cycle 1	Day 1	Pre-Infusion (any time prior to dose); 30±10 minutes after end of infusion [f]	—	Pre-Infusion (any time prior to dose)	—	Predose (any time prior to dose)
	Day 15	—		—	—	Predose (within 15 min prior to dose); 2 hours ±10 min postdose
Cycle 2	Day 1	Pre-Infusion (within 5 hr prior to dose); 30±10 min after end of infusion	Pre-Infusion (within 5 hr prior to dose); 30±10 min after end of infusion	—	Pre-Infusion (any time prior to dose)	—
	Day 15	—	Pre-Infusion (within 5 hr prior to dose)	—	Pre-Infusion (any time prior to dose)	Predose (within 15 min prior to dose); 0.5 hr±5 min postdose, 1 hr±10 min postdose 2 hr±10 min postdose 4 hr±10 min postdose 8 h±30 min postdose
Cycle 4	Day 1	Pre-Infusion (within 5 hr prior to dose); 30±10 min after end of infusion	Pre-Infusion (within 5 hr prior to dose); 30±10 min after end of infusion	—	Pre-infusion (any time prior to dose)	—
	Day 15	—	—	—	—	—

Appendix 2
Pharmacokinetic and Immunogenicity Sampling Schedule for Obinutuzumab, Atezolizumab, and Lenalidomide (cont.)

Study Visit		Serum Obinutuzumab PK Sample [a,b,c]	Serum Atezolizumab PK Sample [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Atezolizumab Anti-Therapeutic Antibody Sample [a]	Plasma Lenalidomide PK Sample [a,d]
Cycle 6	Day 1	Pre-Infusion (within 5 hr prior to dose); 30 ± 10 min after end of infusion	Pre-Infusion (within 5 hr prior to dose)	Pre-Infusion (any time prior to dose)	Pre-Infusion (any time prior to dose)	—
	Day 15	—		—	—	Predose (within 15 min prior to dose); 2 hours ± 10 min postdose
Maintenance (Months 1–24)						
Month 1	Day 1	Pre-Infusion (within 5 hr prior to dose)	Pre-Infusion (within 5 hr prior to dose)	—	Pre-Infusion (any time prior to dose)	—
	Day 2	—	30 min (± 10 min) after end of infusion	—	—	—
Month 2	Day 1	—	—	—	—	—
Month 3	Day 1		—	—	—	—
Month 4	Day 1	—	Pre-Infusion (within 5 hr prior to dose)	—	Pre-Infusion (any time prior to dose)	—
Months 7, 13, and 19	Day 1	Pre-Infusion (within 5 hr prior to dose)	Pre-Infusion (within 5 hr prior to dose)	—	Pre-Infusion (any time prior to dose)	—
Discontinuation and Follow-Up [e]						
Treatment discontinuation		x	x	x	x	—

Appendix 2
Pharmacokinetic and Immunogenicity Sampling Schedule for Obinutuzumab, Atezolizumab, and Lenalidomide (cont.)

Study Visit	Serum Obinutuzumab PK Sample [a,b, c]	Serum Atezolizumab PK Sample [a]	Serum Obinutuzumab HAHA Sample [a]	Serum Atezolizumab Anti-Therapeutic Antibody Sample [a]	Plasma Lenalidomide PK Sample [a, d]
120 days (±30 days) after the last dose of obinutuzumab and the last dose of atezolizumab (as appropriate for the sample)	x	x	x	x	—
1 year after the last dose	x	x	x	x	—

HAHA = human anti-human antibody; PK = pharmacokinetic.

[a] For induction and maintenance, sample collection timing is relative to specified drug.

[b] For induction and maintenance, following analysis of the serum PK 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.

[c] For discontinuation and follow-up, 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.

[d] On lenalidomide PK sampling visits, lenalidomide dose will be taken in the clinic.

[e] An “x” entry indicates that the PK sample is to be taken at any time during the visit.

[f] If the Cycle 1 Day 1 dose of obinutuzumab is split over two days, take the 30-minute, post-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 3
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

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

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

Appendix 3
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to six target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to six dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Appendix 3
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Progressive disease	Progressive metabolic disease	Progressive disease requires at least one of the following
Individual target nodes/nodal masses	Score 4 or 5[b] with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 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 (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisting non-measured lesions

Appendix 3
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

[a] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured; dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

Appendix 3
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

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 4
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 5
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 6
Follicular Lymphoma International Prognostic Index

Table 1 Follicular Lymphoma International Prognostic Index

FLIPI Risk Factor	
Ann Arbor Stage III or IV	
Age $>$60 years	
Serum LDH $>1\times$ULN	
Anemia (hemoglobin $<$120 g/L)	
Involved nodal areas $>$4	
FLIPI Risk Group	**Number of FLIPI Risk Factors**
Low	0 or 1
Intermediate	2
High	3 to 5

FDG = fluorodeoxyglucose; FLIPI = Follicular Lymphoma International Prognostic Index; PET = positron emission tomography; ULN = upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of FLIPI since this prognostic score was established without FDG-PET.

Adapted from: Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma International Prognostic Index. Blood 2004;104:1258–64.

Appendix 6
Follicular Lymphoma International Prognostic Index (cont.)

Table 2 Follicular Lymphoma International Prognostic Index 2

FLIPI2 Risk Factor	
Bone marrow involvement	
Age $>$60 years	
β_2 microglobulin $>1\times$ULN	
Anemia (hemoglobin $<$120 g/L)	
Longest diameter of largest involved node $>$6 cm	
FLIPI2 Risk Group	**Number of FLIPI2 Risk Factors**
Low	0
Intermediate	1 or 2
High	3 to 5

FDG = fluorodeoxyglucose; FLIPI2 = Follicular Lymphoma International Prognostic Index 2; PET = positron emission tomography; ULN = upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of FLIPI2 since this prognostic score was established without FDG-PET.

Adapted from: Federico M, Bellei M, Marcheselli L, et al. Follicular Lymphoma International Prognostic Index 2: a new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 2009;27:4555–62.

Appendix 7
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, 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 8
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 9
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.