

Official Title: A Phase IB/II, Open-Label Study Evaluating the Safety and Pharmacokinetics of GDC-0199 (ABT-199) in Combination With Rituximab (R) or Obinutuzumab (G) Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) in Patients with B-cell Non-Hodgkin's Lymphoma (NHL) and DLBCL

NCT Number: **NCT02055820**

Document Dates: Protocol version 8: 10-Oct-16

PROTOCOL

TITLE: A PHASE IB/II, OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF GDC-0199 (ABT-199) IN COMBINATION WITH RITUXIMAB (R) OR OBINUTUZUMAB (G) PLUS CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE, AND PREDNISONE (CHOP) IN PATIENTS WITH B-CELL NON-HODGKIN'S LYMPHOMA (NHL) AND DLBCL

PROTOCOL NUMBER: GO27878 / NCT02055820

VERSION NUMBER: 8

EUDRACT NUMBER: 2013-003749-40

IND NUMBER: 115045

TEST PRODUCTS: Venetoclax (GDC-0199, ABT-199; RO5537382)
Obinutuzumab (GA101; RO5072759)

MEDICAL MONITOR: [REDACTED], M.D.

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version 1: 17 November 2013

DATES AMENDED: Version 2: 21 January 2014
Version 3: 23 May 2014
Version 4: (France) 2 July 2014
Version 5: 1 October 2014
Version 6: 24 April 2015
Version 7: 7 December 2015
Version 8: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name

[REDACTED]

Title

Company Signatory

Date and Time (UTC)

10-Oct-2016 15:57:30

CONFIDENTIAL

This clinical study is being sponsored globally by F. Hoffmann-La Roche Ltd of Basel, Switzerland. However, it may be implemented in individual countries by Roche's local affiliates, including Genentech, Inc. in the United States. The information contained in this document, especially any unpublished data, is the property of F. Hoffmann-La Roche Ltd (or under its control) and therefore is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from Roche except to the extent necessary to obtain informed consent from persons to whom the drug may be administered.

PROTOCOL AMENDMENT, VERSION 8: RATIONALE

This amendment replaces Version 7 of Protocol GO27878. Changes to the protocol, along with a rationale for each change, are summarized below:

- Venetoclax nonclinical toxicology section updated based on recent data findings
- Twelve month PFS was added as a secondary efficacy objective to align with Section 3.3.3, where it was already included as a secondary efficacy outcome measure (Section 2.2.2).
- Information was added regarding the decision to not open Arm B in Phase II in DLBCL on the basis of information from the GOYA study results (Section 3.2.3).
- The following inclusion/exclusion criteria were updated:
 - Measurable lesions must also be FDG avid on PET to ensure the primary efficacy objective can be assessed and to align with other Roche/Genentech protocols (Section 4.1.2.3).
 - Patients with discordant bone marrow (i.e., low grade histology in bone marrow) may be considered for the study as the outcomes are consistent with DLBCL (per published research) (Section 4.1.3.2).
 - Patients with AST and ALT $> 2.5 \times$ ULN due to disease involvement may be considered for the study as it is expected that lymphoma treatment will normalize these values (Section 4.1.3.3).
 - Primary mediastinal DLBCL will be excluded as primary mediastinal DLBCL has different clinical and pathological features than DLBCL and standard treatment (Section 4.1.3.3).
 - The remission duration as a prerequisite for enrolling a patient with prior malignancy treated with surgery only has been reduced from ≥ 5 years to ≥ 3 years to align with other protocols for comparison (Section 4.1.3.3).
- The recommendation for the low fat breakfast to be consumed prior to venetoclax dosing was modified due to new clinical pharmacology information from other venetoclax studies and to align with other Roche/Genentech protocols (Section 4.3.1.2).
- The guideline for TLS prophylaxis was updated based on a recent analysis of laboratory TLS cases observed in venetoclax studies in NHL and to align with other NHL studies being conducted at Roche/Genentech (Section 4.4.1.5.1).
- Survival Follow-up Section was added to ensure data can be collected for Overall Survival analyses (Section 4.5.7).
- Post-Trial Access to study drugs section was updated to the current protocol template (Section 4.8).
- The [REDACTED] Medical Responsible Contacts Information (Rest of World) was updated to reflect changes to the appointed contacts (Section 5.3.1).

- IPI score criteria was added to Appendix 7 to ensure IPI score is calculated accurately by site staff prior to study entry.
- Double positive (DP) was changed to double expressor (DE) throughout the text as per recent update to WHO nomenclature.
- Section 6.1 (investigator requirements) was updated to remove the exclusion from expedited reporting of anticipated events.

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.

PROTOCOL AMENDMENT, VERSION 8: SUMMARY OF CHANGES

GLOBAL CHANGES

- The term double positive (DP) was replaced with double expressor (DE).
- Abbreviations have been updated, where appropriate, due to the addition of text.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.2.2: Venetoclax Nonclinical Toxicology

The nonclinical toxicology of venetoclax has been evaluated in repeat dose studies of up to 4 weeks' duration with once daily (QD) oral dosing and with up to 4 and 26 week recovery periods in mice and 26 week recovery periods in dogs. In addition, venetoclax has been tested in safety pharmacology studies (cardiovascular [CV], respiratory, and neurofunctional) and in genetic toxicity tests (Ames and in vitro chromosome aberrations assays). A severely toxic dose to 10% of rodents was not identified in mice up to and including the highest dose of 600 mg/kg/day (overall mean area under the concentration time curve [AUC] from Time 0 to 24 hours $[AUC_{0-24}] = 91.5 \mu\text{g} \cdot \text{h/mL}$ and maximum concentration observed $[C_{\text{max}}] = 7.2 \mu\text{g/mL}$). In dogs, the highest non severely toxic dose was 150 mg/kg/day, but as a result of overlapping exposures between the mid and high doses, the highest non severely toxic dose was defined as the mid dose of 50 mg/kg/day (overall mean $AUC_{0-24} = 472 \mu\text{g} \cdot \text{h/mL}$ and $C_{\text{max}} = 27.4 \mu\text{g/mL}$).

Consistent with expected pharmacological activity, venetoclax caused moderate to marked decreases in lymphocytes including both T and B cell subsets, and corresponding lymphoid depletion was observed in the spleen, lymph nodes, gut associated lymphoid tissue (mice), and Peyer's patches (dogs). In dogs after 4-6 months of recovery, B cell counts reversed non dose dependently to 25%-111% of individual baseline (mean reversal to 54% of baseline average). T cell subsets reversed more readily and showed more dose dependence in recovery time and extent. Additional hematological effects included reductions in red cell mass (hemoglobin, hematocrit) that were adverse at 600 mg/kg/day in mice and at 150 mg/kg/day in dogs.

In dogs, venetoclax produced severe decreases in the numbers of spermatogonia after 4 weeks of dosing with progression to severe decreases in all germ cells in testes during the 4 week recovery period. The translatability of the findings to humans is unknown, but this change may be related to venetoclax pharmacology because one or more members of the Bcl-2 family of proteins play a role in spermatogenesis (Yan et al. 2003).

In an anesthetized dog CV model given intravenous (IV) doses of venetoclax, mild reductions in cardiac output (-11% to -19%) and myocardial contractility (dP/dt_{max})

~~–6% to 13%) were observed at plasma concentrations of ≥ 16 $\mu\text{g/mL}$ and ≥ 32 $\mu\text{g/mL}$ respectively, compared with 6 dogs given vehicle; however, no effects on blood pressure, heart rate, or ECG parameters were observed in either the anesthetized dog study or conscious dog CV studies that used telemeterized animals.~~

~~In an ongoing 9 month chronic toxicity study in dogs, change in the hair coat from normal to increased amounts of white hair was observed after 3 months of dosing at 6 or 20 mg/kg/day (mid and high doses, respectively). On the basis of a similar finding of gray hair coat in *BCL2*^{-/-} null mice, the dog hair coat change is likely to be an effect of Bcl 2 inhibition on melanocyte stem cells, but potential effects on patients are unknown. In addition, Bcl 2 in melanocytes might be involved in auditory and retinal protection, and inhibition of Bcl 2 by venetoclax could predispose to hearing loss or visual effects. The meaning of these animal findings for humans is not known, but an event of hearing loss has been reported in 1 patient with chronic lymphocytic leukemia (CLL) who received venetoclax. Patients will be monitored for ocular and auditory findings.~~

~~Other nonclinical findings in dogs included non-severe, cutaneous swelling at high dose, post dose emesis, salivation, and fecal alterations during the dosing period. Microscopic findings of single cell necrosis in the gall bladder epithelium, stomach, exocrine pancreas, and epididymides were considered to be an effect of Bcl 2 inhibition but were of minimal magnitude and not associated with loss of mucosal integrity.~~

~~There were no consistent effects on respiratory or neurological function, and both in vitro genetic toxicity test results were negative.~~

Toxicology assessments completed to date with venetoclax are general toxicology studies with periods of once-daily oral dosing ranging from 2 weeks to 6 months in mice, from 2 weeks to 13 weeks in rats, and from 1 week to 9 weeks in dogs; in vitro and in vivo genetic toxicology; embryo-fetal development in female mice and rabbits; and fertility and early embryonic development in male and female mice. The maximum steady state venetoclax plasma exposures (mean area under the concentration-time curve [AUC]) achieved in the IND-enabling 4 week studies were 92 $\mu\text{g}\cdot\text{h/mL}$ (at 600 mg/kg/day) in mice and 572 $\mu\text{g}\cdot\text{h/mL}$ (at 150 mg/kg/day) in dogs. In the chronic toxicity studies, AUCs reached 34.1 $\mu\text{g}\cdot\text{h/mL}$ (at 300 mg/kg/day) in mice and 86 $\mu\text{g}\cdot\text{h/mL}$ (at 20 mg/kg/day) in dogs. In rats, exposures were higher in females than in males; at dosages of 150 and 400 mg/kg/day in the 13 week maximum tolerated dose study, exposures ranged up to 83.1–127.8 $\mu\text{g}\cdot\text{h/mL}$ in females and up to 26.4–44.2 $\mu\text{g}\cdot\text{h/mL}$ in males.

The primary toxicities associated with venetoclax administration included effects on the hematologic system (decreased lymphocytes and erythrocytes) in mice, rats, and dogs; the male dog reproductive system (testicular germ cell depletion); and embryo-fetal toxicity in mice.

In mice, rats, and dogs, venetoclax produced generally dose-related decreases in lymphocytes in the peripheral blood (of up to 75% in mice, up to 64% in rats, and up to 81% in dogs) and in lymphoid tissues. In dogs, the recovery of lymphocyte counts (total lymphocytes, CD4 + and CD8 + T cells and mature B cells) was prolonged, requiring up to 18 weeks after completion of 2 weeks of dosing. B cells were the most sensitive lymphocyte subtype based on the magnitude of decrease and/or the length of time required for recovery (i.e., 25% –111% of individual baseline; mean reversal to 54% of baseline average). T-cell subsets reversed more readily and showed more dose-dependence in recovery time and extent. Decreases of lymphocytes in lymphoid tissues were reversible in mice and reversible to partially reversible in dogs. Venetoclax-related decreases in lymphocytes in blood and lymphoid tissues are considered pharmacologically-mediated and non-adverse (Marsden and Strasser, 2003).

In the 4 week mouse and dog studies, dose-related reversible decreases in RBC mass were observed. Effects on RBC mass were typified by hemoglobin decreases. At the highest dosages administered, decreases in hemoglobin reached -21% in mice at 600 mg/kg/day and -23% in dogs at 150 mg/kg/day, and were considered to be adverse based on a criterion of -20% decrease. In rats, decreases in hemoglobin were more severe than in mice and dogs at comparable exposures and reached 30% to 49% at ≥ 150 mg/kg/day in females. Hematologic parameters (lymphocyte counts and RBC mass) are readily monitored in clinical trial subjects.

In dogs, venetoclax produced adverse, non-reversible, non-dose-related microscopic findings of testicular germ cell depletion at all dosages tested; there were no testicular effects in mice. The translatability of the testicular findings in dogs to humans is unknown, but this change may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis (Olderied et al. 2001; Sugiyama et al. 2001; Yan et al. 2003). No effects of venetoclax have been identified in female reproductive tissues in mice or dogs in general toxicology studies.

Venetoclax resulted in increased post-implantation loss and decreased fetal body weights in the mouse embryo-fetal development study at the highest dosage administered (150 mg/kg/day); the no-observed-adverse-effect level was defined at the mid-dose of 50 mg/kg/day. Venetoclax was not teratogenic, and there were no other effects on development or fertility.

Additional noteworthy effects of venetoclax included white hair coat discoloration in dogs (occurring after approximately 3 months of dosing in the 9 month study) and single cell necrosis in various epithelial tissues (gallbladder, exocrine pancreas, stomach, exocrine pancreas, and epididymides) in dogs. Single cell necrosis was minimal except for non-dose-dependent minimal to mild single cell necrosis in the pylorus of the stomach at ≥ 2 mg/kg/day in the 9 month study. After 4 weeks of dosing and a 4 week recovery period, reversibility was observed in the gallbladder and exocrine

pancreas, but minimal single cell necrosis was still present in the epididymides and prostate (potentially related to the testicular effects) and in the stomach. Single cell necrosis was considered not to be adverse due to its minimal to mild magnitude and because no loss of mucosal integrity was observed histopathologically. The hair coat change correlated histopathologically with decreased pigment in hair follicle bulbs, and is consistent with the pharmacologic inhibition of Bcl-2 by venetoclax, leading to Bcl-2 functional loss in hair follicle melanocytes dependent on Bcl-2 for survival (Yamamura et al. 1996) A dedicated physical examination of the skin and extensive ophthalmic examinations determined that pigmentation of the skin and in the eye (particularly, the iris and fundus) of the dog appeared unaffected. This was confirmed by the absence of associated histopathologic findings in skin (other than in hair follicles) and in the eye. Consequently, white hair coat discoloration was considered non-adverse; reversibility has not been assessed.

Minor effects of venetoclax were: mild, dose-related, transient post-dose emesis, increased salivation, and fecal alterations (unformed or watery feces); minimally increased pigment in Kupffer cells and macrophages in the liver and gallbladder, respectively; and clinical signs of skin swelling, all in dogs. With regard to the latter finding, dogs at the high dosage of 150 mg/kg/day in the 4 week study had clinical signs of swelling of the skin on the ears, head (cranial area), and forepaws and/or hindpaws. Most but not all animals (8 of 10 dogs) were affected, and in three dogs the swelling reaction was observed after the first dose. The clinical signs were transient and sporadic in occurrence, and were absent during the recovery period. A mechanistic basis for the swelling reactions was not established, but the clinical signs were mild to moderate in severity and reversible, and there were no signs of anaphylaxis.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax, nor was there evidence of phototoxicity.

Venetoclax was tested in a battery of safety pharmacology assays, and produced no effects in the CNS/neurobehavioral or respiratory studies in mice at oral doses up to and including the highest oral dose of 600 mg/kg. No effects on QTc were observed up to a maximum plasma concentration of 46 µg/mL in dogs. In conscious dogs, venetoclax did not produce any cardiovascular effects up to and including the highest oral dose of 150 mg/kg (maximum concentration observed [C_{max}] =16 µg/mL). In the anesthetized dog at higher plasma concentrations, venetoclax produced mild reductions in myocardial contractility (-6% to -13%) and cardiac output (-11% to -19%) at plasma concentrations of ≥16 µg/mL and ≥32 µg/mL, respectively. These concentrations are greater than the plasma concentration of venetoclax in humans (average C_{max} =6.09 µg/mL at the 1200 mg/day dose).

SECTION 2.1: PRIMARY OBJECTIVES

The primary objectives of the Phase II portion of the study are the following:

- To make a preliminary assessment of efficacy as measured by CR rate *at end of treatment* determined by positron emission tomography and/or computed tomography (PET-CT) scans (see Appendix 2) of the combination of venetoclax and R-CHOP administered to patients with previously untreated DLBCL
- To make an assessment of efficacy, as measured by CR rates *at end of treatment* determined by PET-CT scans, of the combination of venetoclax and R-CHOP administered to patients with previously untreated DLBCL co-expressing both Bcl-2 and c-Myc proteins (i.e., ~~DPDE~~-DLBCL)

SECTION 2.2.2: Secondary Efficacy Objective

The secondary efficacy objectives of this study include the following:

- To make a preliminary assessment of efficacy when venetoclax and R-CHOP are administered in combination to patients with previously untreated DLBCL, as measured by:

OR rate

CR rate as determined by CT scan

~~Response duration~~ DOR

PFS

12 month PFS estimate

SECTION 3.1: DESCRIPTION OF THE STUDY

~~After the first 20 patients in the R-CHOP arm of the Phase I portion of the study,~~ *For the Phase II R-CHOP arm portion of the study, after the first 20 patients have completed Cycles 1 and 2 of study treatment,* the Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC; see Section 3.1.1) will meet to review safety data for all patients treated in both the Phase Ib and Phase II portions of the study in order to confirm the safety and tolerability of the combination therapy at the venetoclax dose chosen at the end of Phase Ib.

SECTION 3.1.1: Internal Monitoring Committee and Scientific Oversight Committee

The study will enroll approximately 24–~~48~~60 patients during the dose-finding stage and approximately 180–200 patients in the Phase II portion at approximately 69 investigative sites in North America, the European Union, and Asia Pacific.

SECTION 3.1.2: Phase Ib: Dose-Finding

Each study arm (R-CHOP in Arm A or G-CHOP in Arm B) will have ~~up to~~ four dose-finding cohorts exploring venetoclax doses *and dosing schedule* ranging from 200 to 800 mg- ~~with a maximum dosing administration schedules of a maximum~~ 10 days per cycle.

SECTION 3.1.2.1: Cohort Dosing Regimen

Cycle 1

- Oral dosing of venetoclax will then continue through Day 10 of Cycle 1 and Days 1-10 of Cycles 2 through 8— *or alternative dose administration schedules, that include oral administration of venetoclax on Days 4–8 in Cycle 1 and Days 1–5 in Cycles 2–8.*

SECTION 3.1.2.2: Dose Escalation Guidelines

Dosing with venetoclax will begin on Day 4 of Cycle 1 (or 3 days after the first CHOP dose, see Section 3.1.2.1) and continue to be administered daily through Day 8 *or Day 10* of Cycle 1 and then on *Days 1–5 or Days 1–10* for Cycles 2–8 for up to eight 21-day cycles of combination therapy with R-CHOP or G-CHOP.

If the administration of venetoclax results in unacceptable toxicity on Days 4–10 of Cycle 1 and Days 1–10 of Cycles 2-8 schedule *or other proposed alternative dose administration schedules* then alternative dose regimens of venetoclax (e.g., venetoclax administered on Days 1–3 or 1–7 of 21) or lower doses of venetoclax may be substituted in subsequent cohorts.

SECTION 3.1.3: Phase II: Expansion

Because effects of Bcl-2 inhibition may differ depending on both the level of Bcl-2 expression and the molecular milieu (see Section 1.3), activity of the combination will be explored in specific molecular subsets, including Bcl-2 high, Bcl-2 low, Bcl-2- *overexpression* and c-Myc overexpression (DPE), and GCB and ABC subtypes of DLBCL.

Enrollment into the R-CHOP cohort of patients with both Bcl-2 high and Bcl-2 low DLBCL will continue until approximately 50 patients with ~~DPDE~~-DLBCL (approximately 160–200 patients total; see Section 4.10.6. ~~Patients with Bcl-2 low/negative and c-Myc low DLBCL will be included and ABC versus GCB subset analysis will be performed, but enrollment numbers will not be gated to these groups. Enrollment into the G-CHOP cohort will continue until at least 20 patients have been enrolled.~~

Thereafter, patients will be followed in the clinic every 3 months for safety and disease assessments for up to 2 years after the last patient ~~is enrolled~~ *has completed* treatment or until death or study termination, whichever occurs first.

SECTION 3.1.4: Discontinuation of Venetoclax plus R-CHOP or G-CHOP

Patients who discontinue venetoclax plus R-CHOP or venetoclax plus G-CHOP for reasons other than PD should ~~remain in the study~~ *have a documented response assessment and continue to be followed* until disease progression ~~or even after~~ *institution* of alternative therapy. ~~These patients~~ *se patients* should continue with follow-up visits every 3 months to collect information on disease progression, ~~and /or initiation of an alternative lymphoma therapy, and.~~ *After PD, patients will also continue to be followed for OS yearly* (see Section 4.5.5).

SECTION 3.2.3: Rationale for Venetoclax Dose Selection in the Phase II Portion of the Study

On 17 July 2016, Roche/Genentech as the sponsor of Study BO21005 (Goya study), a Phase III study that evaluated G-CHOP versus R-CHOP in 1L DLBCL, informed through a press release that the primary endpoint of investigator-assessed PFS was not met. Given these results, Arm B (venetoclax +G-CHOP) will not be expanded in Phase II in patients who are first-line with-DLBCL.

SECTION 3.2.9: Rationale for Collecting Tumor Biopsies and Peripheral Blood for Biomarker Studies

The following samples will be collected to enable the evaluation of the parameters listed above:

- *An FFPE tumor biopsy sample must be collected at disease progression and sent to the central laboratory to evaluate venetoclax resistance mechanisms. The sample must be a tissue block or 20 unstained serial slides.*

SECTION 3.4.1.1: Tumor Lysis Syndrome

Hospitalization will be required at initial venetoclax dosing for patients who are determined to be at high risk of TLS as a result of bulky disease (i.e., any lymphoma mass ≥ 10 cm *and/or* evidence of circulating lymphoma cells).

SECTION 3.4.2.1.1: Management of Severe Infusion-Related Reactions

Patients who require close monitoring during the first and all subsequent infusions include patients with preexisting cardiac and pulmonary conditions, patients with prior clinically significant cardiopulmonary adverse events, and patients with high numbers of circulating malignant cells ($\geq 25,000$ cells/ μ L) with or without evidence of high tumor burden.

SECTION 3.4.2.2: Tumor Lysis Syndrome

The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells ($\geq 25,000$ cells/ μ L) or high tumor burden.

SECTION 4.1.2.3: All Patients

Patients must meet the following criteria for study entry:

- At least one bi-dimensionally measurable *lymphoma* lesion on CT scan defined as > 1.5 cm in its longest dimension, *which is also FDG avid by screening PET scan.*
- Adequate hematologic function (unless caused by underlying disease, as established by extensive bone marrow involvement or as a result of hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator) defined as follows:

Hemoglobin ≥ 9 g/dL

Absolute neutrophil count ANC $\geq 1.5 \times 10^9/L$

SECTION 4.1.3.2: Patients Enrolled in the Phase II Portion of the Study

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

- Patients with transformed lymphoma (*patients with discordant bone marrow involvement (i.e., low grade histology in bone marrow) may be considered after discussion with the Medical Monitor*)

SECTION 4.1.3.3: All Patients

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

- CNS lymphoma *or primary mediastinal DLBCL*
- History of other malignancy that could affect compliance with the protocol or interpretation of results
 - Patients with a malignancy that has been treated with surgery alone with curative intent will also be excluded, unless the malignancy has been in documented remission without treatment for ≥ 53 years prior to enrollment.
- Received the following agents within 7 days prior to the first dose of venetoclax:
 - ~~Steroid therapy for anti-neoplastic intent within 7 days prior to the first dose of study drug.~~ *Cycle 1 Day 1. See steroid use guidelines in Section 4.4.1 for specific exceptions.*
- Any of the following abnormal laboratory values:
 - AST or ALT $> 2.5 \times$ ULN (unless due to disease involvement; Medical Monitor to be consulted prior to enrollment)

SECTION 4.3.1.2: Dosage, Administration, and Storage

Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of ~~a low fat~~ breakfast or the patient's first meal of the day. *A meal containing approximately 30% of the total caloric content from fat is recommended to ensure adequate absorption of venetoclax. On days that pre-dose PK sampling is required, the patient's first meal of the day (e.g., breakfast) will be consumed in the morning at the clinic, and venetoclax dosing will occur in the morning clinic after the completion of a low fat breakfast the meal or the patient's first meal of the day at the clinic to facilitate PK sampling. Examples of a low fat breakfast include 2 slices of white toast with 1 tablespoon of low fat margarine and 1 tablespoon of jelly and 8 ounces of skim milk (319 calories and 8.2 g fat) or 1 cup of cereal, 8 ounces of skim milk, 1 slice of toast with jam, apple juice, and 1 cup of coffee or tea (520 calories and 2 g fat).*

The recommended breakfast is as follows:

- 1 box cereal (30–40 g)*
- Skim milk (240 mL)*
- 1 boiled egg*
- 1 slice toast (15 g)*

Margarine (10 g)

Total calories should be approximately 520 Kcal; 30% of the total caloric content of the meal is from fat. Total grams of fat should be approximately 17 grams.

SECTION 4.3.3.8: Management of Infusion Related Reactions and Anaphylaxis

Table 2 Management of Infusion-Related Symptoms

Infusion-Related Symptoms ^a	Guidance
Grades 1 and 2	Slow or withhold infusion. Give supportive treatment ^b . Upon symptom resolution, may resume infusion-rate escalation.
Grade 3	Discontinue infusion. Give supportive treatment ^b . Upon symptom resolution, may resume infusion rate escalation. Note: If the same adverse event recurs with same severity, treatment must be permanently discontinued.
Grade 4	Discontinue infusion immediately, treat symptoms aggressively, and do not restart drug.

IV=intravenous.

^a Refer to National Cancer Institute Common Terminology Criteria for Adverse Events, (Version 4.0) for the grading of symptoms. This table does not refer to management of IgE-mediated allergic reactions, which should be managed as directed in Section 4.4.1.6.

^b Supportive treatment: Patients should be treated with acetaminophen and an antihistamine such as diphenhydramine hydrochloride if they have not been received in the previous 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg of IV prednisolone or equivalent), and/or bronchodilators. For hypotension, patients may require vasopressors.

SECTION 4.3.5: Administration of Granulocyte Colony-Stimulating Factor

All patients must receive G-CSF as primary prophylaxis for neutropenia starting with Cycle 1 and continuing through each additional cycle of ~~study~~CHOP therapy received.

SECTION 4.4.1: Concomitant Therapy

Steroid use not otherwise dictated by the protocol CHOP treatment will follow the guidelines outlined below:

- Corticosteroid use >30 mg/day of prednisone or equivalent: Not allowed within 7 days prior to ~~first dose~~Cycle 1 Day 1 except as specified below

SECTION 4.4.1.3: Treatment and Prophylaxis of Neutropenia

G-CSF should be administered as primary prophylaxis starting with Cycle 1 of therapy *and continue through each cycle of CHOP therapy received* for all patients unless there is a medical contraindication or the investigator feels it is not in the patient's best interest to receive G-CSF.

SECTION 4.4.1.5: Prophylaxis for Tumor Lysis Syndrome

TLS is a risk for patients with NHL who are treated with high cell-killing agents. *The risk of TLS is a continuum based on multiple factors that include tumor burden and comorbidities. Risk is highest for those with bulky disease, elevated absolute lymphocyte count, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, compromised renal function, and dehydration. Patients* All patients should undergo tumor burden assessment with bulky disease, defined as any lymph node ≥ 8 cm on the screening CT scan, and/or lymphocytosis due to circulating lymphoma cells, are considered at higher risk of TLS and must be hospitalized for more intensive monitoring during the initial dose, CBC with WBC differential, and blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine). Pre-existing chemistry abnormalities should be corrected prior to initiation of treatment with venetoclax.

SECTION 4.4.1.5.1: Hospitalization

Patients exhibiting specific characteristics at higher screening or initiation of venetoclax treatment are considered to be at high risk for development of TLS (and must be hospitalized for more intensive prophylaxis and monitored during for the initial dose of venetoclax. These patients are identified by the presence of any of the following:

- Any lymph node ≥ 8 cm and/or mass ≥ 10 cm and/or on the screening CT scan
- Circulating lymphoma cells) must be hospitalized for the initial dose of venetoclax. defined by ~~Out-of-range~~ (high) absolute lymphocyte count (ALC) or the presence of abnormal cells in the peripheral blood differential signifying circulating lymphoma cells

In addition to characteristics requiring mandatory hospitalization, other patient characteristics may suggest an increased risk of TLS. These include but are not limited to the following:

- Overall disease burden (e.g., several enlarged lymph nodes, even if none reaching 10 cm)
- Elevated LDH levels
- Compromised renal function, as evidenced by low CRCL
- Extensive bone marrow involvement
- Dehydration

Hospitalization ~~should also be considered~~ is not mandatory for patients who exhibit these characteristics, but these and any other factors that are considered relevant to TLS should be considered in the overall assessment of the patient's state and their risk to develop TLS. Investigators should use their judgment in their assessment of the patient's risk of TLS development and may choose to hospitalize any patient they consider to be at risk for the development of TLS during the first dose of venetoclax,

with creatinine clearance ≤ 80 mL/min, in discussion with the Medical Monitor. *approval of the Medical Monitor.*

SECTION 4.4.1.8: Other Concomitant Medications

G-CSF will be administered as primary prophylaxis in each cycle of *CHOP* therapy (see Section 4.4.1.3).

SECTION 4.4.2: Excluded Therapy

Table 4 Excluded and Cautionary Medications

Excluded Medications
Anti-cancer therapies including chemotherapy, radiotherapy, or other investigational therapy, including targeted small molecule agents: Excluded 5 half-lives <i>28 days</i> prior to first dose and throughout venetoclax administration.
Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent: Excluded 8 weeks prior to first dose and throughout venetoclax administration
Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit: Excluded 3 days prior to first dose and throughout venetoclax administration

SECTION 4.5.1.4: Tumor and Response Evaluation

All measurable disease must be documented at screening by a ~~Diagnostic quality CT scan and a combined PET-CT scan~~ *with a diagnostic quality CT component.* ~~and re-assessed at each subsequent tumor evaluation.~~ Response assessments will be determined by the investigator on the basis of imaging studies and bone marrow examinations (if appropriate), with the use of the modified Lugano Classification (Cheson et al. 2014; see Appendix 2). *A five-point scale score is required as part of the PET scan response.*

Patients will be evaluated for disease response by PET-CT imaging after Cycle 4 and at 6 to 8 weeks after Day 1 of Cycle 8 *or last cycle received*. A bone marrow examination must be repeated ~~only to confirm a CR if it was previously positive, if it was not performed, or if it was indeterminate at screening.~~

Diagnostic-quality CT scan with use of oral and IV contrast (unless medically contraindicated) must be obtained at baseline, *after Cycle 4* and at end of treatment evaluation (6 to 8 weeks after Day 1 of Cycle 8 *or last cycle received*). If PET-CT with diagnostic CT is not obtainable, a separate diagnostic CT scan must be performed at these ~~two~~ timepoints in addition to the PET scans.

CT scans (with oral and IV contrast, unless medically contraindicated) will be performed every 6 months for 2 years and as clinically indicated *during these follow ups*. If a

patient exhibits clinical signs of possible disease progression (i.e., increased or de novo enlargement of liver, spleen or lymph nodes on physical examination), additional assessments including PET-CT or contrast-enhanced CT scan and/or bone marrow must be performed to evaluate for PD.

CT scans (with contrast) should include chest, abdomen, and pelvis scans; CT scans of the neck should be included if clinically indicated (*MRIs may be used instead of CT scans in patients for whom CT scans are contraindicated*). CT scans for response assessment may be limited to areas of prior involvement only if required by local regulatory authorities. ~~Provision will be made to collect and store the CT scans should a radiology review be required in the future.~~

Bone marrow examinations should include biopsy and/or aspirate for morphology and flow cytometry and are required at screening. ~~If positive or indeterminate at screening, a subsequent bone marrow examination is required only to confirm a CR.~~

SECTION 4.5.1.5.1: Central Laboratory Assessments

- PK assays

Serum samples will be obtained for measurement of *rituximab* or obinutuzumab concentrations and EDTA-anticoagulated; plasma samples will be obtained for measurement of venetoclax or *CHOP* concentrations at timepoints noted in Appendix 3. *The samples will be sent to the central laboratory and then to a Sponsor designated bioanalytical laboratory or to the Sponsor or designee for analysis. Relevant biotransformation products of study treatment may also be analyzed at the discretion of the Sponsor.*

SECTION 4.5.2: Screening and Pretreatment Assessments

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 21 days prior to first dose of study drug may be used (bone marrow examination could have been performed up to 3 months prior to Cycle 1 Day 1, ~~if the laboratory report is available and if the tumor biopsy sample can be obtained from initial diagnosis~~); such tests do not need to be repeated for screening.

SECTION 4.5.6: Follow-Up Assessments

Patients will be followed for response until disease progression, death, ~~initiation of another NHL therapy~~, or study closure, whichever occurs first. ~~Study closure will occur approximately 2 years after the last patient has been enrolled.~~

SECTION 4.5.7: Survival Follow-Up Assessments

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until death, lost to follow-up, consent withdrawal, or study termination by Roche, whichever occurs first. All patients will be followed for survival and new anti-lymphoma therapy information unless the patient requests to be withdrawn from follow-up (this request must be

documented in the source documents and signed by the investigator), is lost to follow-up, dies, or the study is terminated by the Sponsor, whichever occurs first. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only if permitted per local regulations.

Study closure will occur approximately 2 years after the last patient has completed treatment.

SECTION 4.8: POST-STUDY ACCESS TO VENETOCLAX, OBINUTUZUMAB, AND RITUXIMAB

~~Continued access to venetoclax, CHOP, rituximab, and/or obinutuzumab is not guaranteed after the end of the study. After the patient's participation in the study ends, the patient or the patient's health plan will need to pay for medicines and clinic, hospital, and doctors' services that are part of the patient's regular medical care.~~

The Sponsor will offer post-study access to the study drug (venetoclax, obinutuzumab, and rituximab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being*
- There are no appropriate alternative treatments available to the patient*
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)*
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for NHL/DLBCL*
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for NHL/DLBCL*
- Provision of study drug is not permitted under the laws and regulations of the patient's country*

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

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

SECTION 4.10.4.1: Tumor Assessment Data

~~ITT population and~~ All patients in the extension cohort who receive any amount of venetoclax or R-CHOP/G-CHOP will be included in the activity analysis.

SECTION 4.10.4.2: Interim Analyses

An extension of the predictive probability design (Lee and Liu 2008) will be used to guide stopping by comparing CR rates in the venetoclax + R-CHOP arm with historical controls using R-CHOP.

SECTION 4.10.6: Determination of Sample Size

~~The sample size of 20 for the G-CHOP + venetoclax Arm in the Phase II portion is expected to be sufficient to obtain a preliminary estimate of the percentage of patients with compromised chemotherapy dose intensity.~~

SECTION 5.1: SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events including serious adverse events, ~~selected adverse events upon emerging data,~~ and adverse events of special interest, measurement of protocol-specified safety laboratory assessments, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

SECTION 5.1.2: Serious Adverse Event (Immediately Reportable to the Sponsor)

“Serious” is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately *via the Adverse Event eCRF* (i.e., no more than 24 hours after learning of the event; see Section 5.3.2 for reporting instructions).

SECTION 5.1.3: 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 *via the Adverse Event eCRF* (i.e., no more than 24 hours after learning of the event; see Section 5.3.2 for reporting instructions).

SECTION 5.2.1: Adverse Event Reporting Period

After this period, the investigator should report any *deaths*, serious adverse events or adverse events of special interest that are believed to be related to prior study drug treatment (see Section 5.5).

SECTION 5.2.5.11: Hospitalization or Prolonged Hospitalization

The following hospitalization scenarios are not considered to be adverse events:

- *Planned hospitalization* Required by the protocol (e.g., to provide TLS prophylaxis or monitoring without significant clinical sequelae, or to perform an efficacy measurement for the study)

SECTION 5.3: IMMEDIATE REPORTING REQUIREMENTS FROM THE 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; *via the Adverse Event eCRF*; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event.

The investigator must report new significant follow-up information for these events to the Sponsor immediately *via the Adverse Event eCRF* (i.e., no more than 24 hours after becoming aware of the information).

SECTION 5.3.1: Emergency Medical Contacts

██████████ Medical Responsible Contact Information (Rest of World)

Medical Advisor (based in Spain): ██████████, M.D.

Telephone Number: ██████████

Medical Advisor (based in Singapore): ██████████, M.D.

Telephone Number: ██████████

SECTION 5.3.2: Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

SECTION 5.3.2.2: Events Occurring after Initiation of Study Drug

After initiation of study drug, serious adverse events and ~~non-serious~~ adverse events of special interest will be reported through 30 days after the last dose of venetoclax or CHOP or 90 days after the last dose of rituximab or obinutuzumab, whichever is later.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form and fax cover sheet should be completed and faxed *or scanned and emailed* to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

SECTION 5.3.3.1: Pregnancies in Female Patients

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed *or scanned and emailed* to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy) with use of the fax numbers provided to

investigators (see "Protocol Administrative and Contact Information & List of Investigators").

SECTION 5.5: POST-STUDY ADVERSE EVENTS

At the time of *study treatment* completion or *study treatment* discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should report these events directly to Roche Safety Risk Management via telephone or via fax machine *or scanned and emailed* with the use the Serious Adverse Event/Adverse Event of Special Interest Reporting Form and fax cover sheet (see "Protocol Administrative and Contact Information & List of Investigators").

SECTION 5.6: EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

~~Certain adverse events (e.g., known consequences of the underlying disease or common co-morbidities in the study population) are anticipated to occur in the study population at some frequency independent of drug exposure and will be excluded from expedited reporting. A list of such anticipated events will be provided to drug safety operations and to health authorities upon request.~~

~~Although exempted from expedited reporting to certain health authorities and IRBs/ECs as individual cases, these Serious Adverse Events must be reported to the Sponsors within 24 hours of the site being made aware of the serious adverse event as defined in Section 5.3.2.~~

REFERENCES

Three references were added and one deleted to support added or modified text in the amendment.

APPENDIX 1: Schedule of Assessments

The Schedule of Assessments has been revised to reflect the changes to the protocol.

APPENDIX 2: The Modified Lugano Classification: Revised Criteria for Response Assessment

The Lugano Classification described by Cheson (2014), is presented in the Revised Criteria for Response Assessment table with the following modifications: (1) For complete response (CR), if the bone marrow was involved by lymphoma *or indeterminate* prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy; (2) For PET-CT-based partial response (PR), CT criteria for PR (or CR) must also be met.

The table in Appendix 2 was updated to reflect these modifications.

APPENDIX 3: Pharmacokinetic Samples

The word “blood” was added to each of the table titles:

Table 1 Pharmacokinetic *Blood* Sampling for Venetoclax+R-CHOP (ARM A) in Phase I

Table 2 Pharmacokinetic *Blood* Sampling for Venetoclax+G-CHOP (Arm B) in Phase I

Table 3 Pharmacokinetic *Blood* Sampling in Phase II for Approximately the First 20 Patients in Arm A

Table 4 Pharmacokinetic Blood Sampling in Remaining Phase II Patients

Footnote C was modified:

Note that the window for the participating sites must be adjusted to -2+1 day (rather than ± 2 days) for this visit ~~in order to get an appropriate pre-dose PK sample.~~

APPENDIX 7: International Prognostic Index and Ann Arbor Staging Classification

Appendix 7 was added.

International Prognostic Index

The International Prognostic Index for aggressive non-Hodgkin’s lymphoma identifies five significant risk factors that are prognostic of overall survival (OS):

<i>Risk Factors</i>	
<i>Ann-Arbor Stage III or IV</i>	
<i>Age >60 years</i>	
<i>Elevated LDH</i>	
<i>ECOG performance status ≥ 2</i>	
<i>Extranodal involvement ≥ 2</i>	
<i>IPI Risk Group</i>	<i>Number of IPI Risk Factors</i>
<i>Low</i>	<i>0 or 1</i>
<i>Low-intermediate</i>	<i>2</i>
<i>High-intermediate</i>	<i>3</i>
<i>High</i>	<i>4 or 5</i>

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index.

Ann Arbor Staging Classification for Hodgkin and Non-Hodgkin's Lymphoma

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	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

^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.

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.

Clinical stage refers to the extent of disease determined by diagnostic tests following a single diagnostic biopsy. If a second biopsy of any kind is obtained, even if negative, the term pathologic stage is used.

Adapted from:

1. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. *Cancer Res* 1971;31:1860-1.
2. 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.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM	31
PROTOCOL SYNOPSIS	32
1. BACKGROUND	46
1.1 Background on Disease.....	46
1.1.1 Indolent Non-Hodgkin’s Lymphoma.....	46
1.1.2 Diffuse Large B-Cell Lymphoma	46
1.2 Background on the Molecules	48
1.2.1 Bcl-2 Protein Family	48
1.2.2 Venetoclax.....	48
1.2.2.1 Venetoclax Nonclinical Activity and Pharmacokinetic Profile	48
1.2.2.2 Venetoclax Nonclinical Toxicology	49
1.2.2.3 Venetoclax Clinical Experience	52
1.2.2.4 Clinical Pharmacokinetics and Pharmacodynamics	54
1.2.3 Obinutuzumab	55
1.2.3.1 Obinutuzumab Mechanism of Action	55
1.2.3.2 Obinutuzumab Nonclinical Toxicology	55
1.2.3.3 Obinutuzumab Nonclinical Efficacy	56
1.2.3.4 Obinutuzumab Clinical Experience.....	57
1.2.3.5 Obinutuzumab Pharmacokinetics and Pharmacodynamics	58
1.3 Study Rationale	58
2. OBJECTIVES.....	59
2.1 Primary Objectives	59
2.2 Secondary Objectives.....	60
2.2.1 Pharmacokinetic Objectives	60
2.2.2 Secondary Efficacy Objectives	60
2.2.3 Exploratory Objectives.....	61
3. STUDY DESIGN	61
3.1 Description of the Study.....	61

3.1.1	Internal Monitoring Committee and Scientific Oversight Committee	62
3.1.2	Phase Ib: Dose-Finding	64
3.1.2.1	Cohort Dosing Regimen	64
3.1.2.2	Dose-Escalation Guidelines.....	65
3.1.2.3	Dose-Escalation Rules and Determination of Dose-Limiting Toxicity.....	66
3.1.2.4	Definition of Dose-Limiting Toxicity.....	67
3.1.3	Phase II: Expansion.....	68
3.1.4	Discontinuation of Venetoclax Plus R-CHOP or G-CHOP	69
3.2	Rationale for Study Design	70
3.2.1	Benefit/Risk Assessment.....	70
3.2.2	Rationale for Venetoclax Dose Selection in the Phase I Portion of the Study	71
3.2.3	Rationale for Venetoclax Dose Selection in the Phase II Portion of the Study	72
3.2.4	Rationale for R-CHOP Dosing	73
3.2.5	Rationale for G-CHOP Dosing.....	73
3.2.6	Rationale for Dosing Schedule	74
3.2.7	Rationale for Treatment of Patients with Previously Untreated DLBCL.....	75
3.2.8	Rationale for Pharmacokinetic Assessments.....	75
3.2.9	Rationale for Collecting Tumor Biopsies and Peripheral Blood for Biomarker Studies.....	76
3.3	Outcome Measures	77
3.3.1	Safety Outcome Measures	77
3.3.2	Pharmacokinetic Outcome Measures.....	78
3.3.3	Efficacy Outcome Measures.....	78
3.3.4	Exploratory Assessments	79
3.4	Safety Plan	79
3.4.1	Risks Associated with Venetoclax and Their Management.....	80
3.4.1.1	Tumor Lysis Syndrome.....	80
3.4.1.2	Cytopenias.....	80

3.4.1.3	Infections	80
3.4.1.4	Decreased Spermatogenesis	81
3.4.1.5	Drug-Drug Interaction	81
3.4.2	Risks Associated with Rituximab Therapy and Their Management	81
3.4.2.1	Infusion-Related Reactions.....	81
3.4.2.2	Tumor Lysis Syndrome.....	82
3.4.2.3	Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections	82
3.4.2.4	Cardiovascular Events.....	83
3.4.2.5	Bowel Obstruction and Perforation.....	83
3.4.2.6	Immunization	84
3.4.3	Risks Associated with Obinutuzumab Therapy.....	84
3.4.3.1	Infusion-Related Reactions and Hypersensitivity Reactions (Including Anaphylaxis).....	84
3.4.3.2	Tumor Lysis Syndrome.....	85
3.4.3.3	Thrombocytopenia and Neutropenia	85
3.4.3.4	Anti-Therapeutic Antibody	85
3.4.3.5	Infection.....	86
3.4.3.6	Gastrointestinal Perforation	86
3.4.4	Risks Associated with CHOP Chemotherapy	86
3.4.5	Risks Associated with the Combination of Venetoclax plus R-CHOP or G-CHOP.....	86
3.5	Ethical Considerations	87
3.6	Administrative Structure.....	88
3.7	Independent Review Committee.....	88
3.8	Compliance with Laws and Regulations	88
4.	MATERIALS AND METHODS	89
4.1	Patients.....	89
4.1.1	Patient Selection.....	89
4.1.2	Inclusion Criteria.....	89
4.1.2.1	Patients Enrolled in the Dose-Finding Portion of the Study	89

4.1.2.2	Patients Enrolled in the Phase II Portion of the Study	89
4.1.2.3	All Patients.....	89
4.1.3	Exclusion Criteria	90
4.1.3.1	Patients Enrolled in the Dose-Finding Portion of the Study	90
4.1.3.2	Patients Enrolled in the Phase II Portion of the Study	90
4.1.3.3	All Patients.....	90
4.1.4	Criteria for Tumor Biopsy Tissue	92
4.2	Method of Treatment Assignment.....	93
4.3	Study Treatment.....	94
4.3.1	Venetoclax.....	94
4.3.1.1	Formulation.....	94
4.3.1.2	Dosage, Administration, and Storage	94
4.3.1.3	Dosage Delays and Modification	95
4.3.2	Rituximab.....	95
4.3.2.1	Formulation.....	95
4.3.2.2	Dosage, Administration, and Storage	95
4.3.2.3	Dosage Modification	96
4.3.3	Obinutuzumab	97
4.3.3.1	Formulation.....	97
4.3.3.2	Handling and Storage	97
4.3.3.3	Obinutuzumab Dose and Schedule	97
4.3.3.4	Obinutuzumab Preparation.....	97
4.3.3.5	Obinutuzumab Administration.....	98
4.3.3.6	Premedication.....	99
4.3.3.7	Management of Tumor Lysis Syndrome	100
4.3.3.8	Management of Infusion-Related Reactions and Anaphylaxis	100
4.3.3.9	Cardiac or Pulmonary Events	101
4.3.3.10	Dosage Modification or Delay.....	101
4.3.4	CHOP Chemotherapy.....	101
4.3.4.1	Dosage and Administration.....	101

4.3.4.2	Dosage Modification or Delay	102
4.3.5	Administration of Granulocyte Colony-Stimulating Factor	102
4.3.6	Dosage Delays and Modifications	102
4.3.6.1	Dosage Delays and Modifications: Venetoclax, Rituximab, Obinutuzumab, and CHOP Chemotherapy	102
4.3.7	Permanent Treatment Discontinuation Criteria.....	109
4.3.7.1	Permanent Treatment Discontinuation Criteria for Venetoclax.....	109
4.3.7.2	Permanent Treatment Discontinuation Criteria for Rituximab or Obinutuzumab	109
4.3.7.3	R-CHOP or G-CHOP Chemotherapy.....	109
4.4	Concomitant and Excluded Therapies	109
4.4.1	Concomitant Therapy	109
4.4.1.1	CNS Prophylaxis	110
4.4.1.2	Prophylaxis for Hemorrhagic Cystitis	110
4.4.1.3	Treatment and Prophylaxis of Neutropenia	110
4.4.1.4	Premedication before Rituximab or Obinutuzumab Therapy	111
4.4.1.5	Prophylaxis for Tumor Lysis Syndrome	111
4.4.1.6	Infection Prophylaxis	113
4.4.1.7	Monitoring and Treatment for Hepatitis B Reactivation.....	113
4.4.1.8	Other Concomitant Medications	114
4.4.2	Excluded Therapy.....	115
4.5	Study Assessments	117
4.5.1	Definitions of Study Assessments	117
4.5.1.1	Medical History and Demographics	117
4.5.1.2	Vital Signs.....	117
4.5.1.3	Physical Examination	117
4.5.1.4	Tumor and Response Evaluation	117
4.5.1.5	Laboratory Assessments	118
4.5.1.6	Electrocardiogram	119
4.5.1.7	MUGA/Echocardiogram.....	119

4.5.2	Screening and Pretreatment Assessments.....	119
4.5.3	Roche Clinical Repository.....	120
4.5.3.1	Overview of the Roche Clinical Repository.....	120
4.5.3.2	Approval by the Institutional Review Board or Ethics Committee	120
4.5.3.3	Sample Collection.....	121
4.5.3.4	Confidentiality.....	121
4.5.3.5	Consent to Participate in the Roche Clinical Repository	122
4.5.3.6	Withdrawal from the Roche Clinical Repository.....	122
4.5.3.7	Monitoring and Oversight.....	122
4.5.4	Assessments during Treatment.....	123
4.5.5	End of Treatment Visit	123
4.5.6	Follow-Up Assessments	123
4.5.7	Survival Follow-Up Assessments	123
4.6	Patient Discontinuation	124
4.7	Study Discontinuation	124
4.8	Post-Study Access to Venetoclax, Obinutuzumab, and Rituximab.....	124
4.9	Assay Methods	125
4.10	Statistical Methods	125
4.10.1	Analysis of the Conduct of the Study	126
4.10.2	Safety Analyses	126
4.10.3	Pharmacokinetic and Pharmacodynamic Analyses	126
4.10.4	Activity Analyses.....	127
4.10.4.1	Tumor Assessment Data	127
4.10.4.2	Interim Analyses	127
4.10.4.3	Predictive Diagnostics	128
4.10.5	Exploratory Analyses.....	128
4.10.6	Determination of Sample Size	128
4.11	Data Quality Assurance	129
5.	ASSESSMENT OF SAFETY.....	129
5.1	Safety Parameters and Definitions	129

5.1.1	Adverse Event	130
5.1.2	Serious Adverse Event (Immediately Reportable to the Sponsor)	130
5.1.3	Adverse Events of Special Interest (Immediately Reportable to the Sponsor).....	131
5.2	Methods and Timing for Capturing and Assessing Safety Parameters.....	131
5.2.1	Adverse Event Reporting Period	132
5.2.2	Eliciting Adverse Events	132
5.2.3	Assessment of Severity of Adverse Events	132
5.2.4	Assessment of Causality of Adverse Events	133
5.2.5	Procedures for Recording Adverse Events.....	134
5.2.5.1	Infusion-Related Reactions.....	134
5.2.5.2	Diagnosis versus Signs and Symptoms.....	134
5.2.5.3	Adverse Events Occurring Secondary to Other Events.....	135
5.2.5.4	Persistent or Recurrent Adverse Events.....	135
5.2.5.5	Abnormal Laboratory Values	136
5.2.5.6	Abnormal Vital Sign Values	136
5.2.5.7	Abnormal Liver Function Tests	137
5.2.5.8	Deaths	137
5.2.5.9	Preexisting Medical Conditions.....	138
5.2.5.10	Lack of Efficacy or Worsening of Lymphoma.....	138
5.2.5.11	Hospitalization or Prolonged Hospitalization.....	138
5.2.5.12	Adverse Events Associated with an Overdose or Error in Drug Administration	139
5.3	Immediate Reporting Requirements from Investigator to Sponsor.....	139
5.3.1	Emergency Medical Contacts	140
5.3.2	Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest.....	140
5.3.2.1	Events Occurring prior to Initiation of Study Drug.....	140
5.3.2.2	Events Occurring after Initiation of Study Drug.....	140
5.3.3	Reporting Requirements for Pregnancies.....	141
5.3.3.1	Pregnancies in Female Patients	141

5.3.3.2	Pregnancies in Female Partners of Male Patients	142
5.3.3.3	Abortions	142
5.3.3.4	Congenital Anomalies/Birth Defects	142
5.4	Follow-Up of Patients after Adverse Events	142
5.4.1	Investigator Follow-Up	142
5.4.2	Sponsor Follow-Up	143
5.5	Post-Study Adverse Events	143
5.6	Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees.....	143
6.	INVESTIGATOR REQUIREMENTS.....	144
6.1	Study Initiation	144
6.2	Study Completion	145
6.3	Informed Consent Form.....	145
6.3.1	Optional Research Informed Consent	146
6.4	Communication with the Institutional Review Board or Ethics Committee.....	146
6.5	Study Monitoring Requirements	147
6.6	Electronic Case Report Forms.....	147
6.7	Source Data Documentation.....	147
6.8	Use of Computerized Systems	148
6.9	Study Medication Accountability	148
6.10	Disclosure of Data	149
6.11	Retention of Records.....	149
7.	REFERENCES	150

LIST OF TABLES

Table 1	Administration of First and Subsequent Infusions of Obinutuzumab.....	99
Table 2	Management of Infusion-Related Symptoms	101
Table 3	Guidelines for Dose Delay or Modification of Venetoclax, Rituximab, or Obinutuzumab and CHOP Chemotherapy	104
Table 4	Excluded and Cautionary Medications.....	116

Table 5	95% Confidence Intervals for Expected Observed Rates for Sample Sizes	129
Table 6	Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE	133
Table 7	Causal Attribution Guidance	134

LIST OF FIGURES

Figure 1	Study Schema.....	63
Figure 2	Venetoclax Dose-Finding Cohorts	66

LIST OF APPENDICES

Appendix 1	Schedule of Assessments.....	154
Appendix 2	The Modified Lugano Classification: Revised Criteria for Response Assessment	159
Appendix 3	Pharmacokinetic Samples.....	164
Appendix 4	Anaphylaxis Management.....	167
Appendix 5	Sample List of Excluded and Cautionary Medications	168
Appendix 6	Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax	169
Appendix 7	International Prognostic Index and Ann Arbor Staging Classification.....	173

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: A PHASE IB/II, OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF GDC-0199 (ABT-199) IN COMBINATION WITH RITUXIMAB (R) OR OBINUTUZUMAB (G) PLUS CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRIStINE, AND PREDNISONE (CHOP) IN PATIENTS WITH B-CELL NON-HODGKIN'S LYMPHOMA (NHL) AND DLBCL

PROTOCOL NUMBER: GO27878

VERSION NUMBER: 8

EUDRACT NUMBER: 2013-003749-40

IND NUMBER: 115045

TEST PRODUCTS: Venetoclax (GDC-0199, ABT-199; RO5537382)
Obinutuzumab (GA101; RO5072759)

MEDICAL MONITOR: [REDACTED], M.D.

SPONSOR: F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

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

PROTOCOL SYNOPSIS

TITLE: A PHASE IB/II, OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF GDC-0199 (ABT-199) IN COMBINATION WITH RITUXIMAB (R) OR OBINUTUZUMAB (G) PLUS CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRIStINE, AND PREDNISONE (CHOP) IN PATIENTS WITH B-CELL NON-HODGKIN'S LYMPHOMA (NHL) AND DLBCL

PROTOCOL NUMBER: GO27878

VERSION NUMBER: 8

EUDRACT NUMBER: 2013-003749-40

IND NUMBER: 115045

TEST PRODUCTS: Venetoclax (GDC-0199, ABT-199)
Obinutuzumab (GA101; RO5072759)

PHASE: Ib/II

INDICATION: B-cell non-Hodgkin's lymphoma

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives

Primary Efficacy Objectives

The primary objective of the Phase I portion of the study is the following:

- To estimate the maximum tolerated dosing schedule for venetoclax given in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP) to patients with B-cell non-Hodgkin's lymphoma (NHL), either previously untreated or relapsed/refractory after a maximum of one prior therapy

The primary objectives of the Phase II portion of the study are the following:

- To assess the safety and tolerability of the combination of venetoclax and R-CHOP or G-CHOP administered to patients with previously untreated diffuse large B-cell lymphoma (DLBCL)
- To make a preliminary assessment of efficacy as measured by complete response (CR) rate *at end of treatment* determined by positron emission tomography and/or computed tomography (PET-CT) scans of the combination of venetoclax and R-CHOP administered to patients with previously untreated DLBCL
- To make an assessment of efficacy, as measured by CR rates *at end of treatment* determined by PET-CT scans, of the combination of venetoclax and R-CHOP administered to patients with previously untreated DLBCL co-expressing both Bcl-2 and c-Myc proteins (i.e., double expressor (DE)-DLBCL)

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives of this study are the following:

- To characterize the pharmacokinetics of venetoclax and relevant metabolites when administered in combination with R-CHOP or G-CHOP in the relapsed/refractory or previously untreated setting in NHL
- To characterize the pharmacokinetics of rituximab, obinutuzumab, and prednisone when administered in combination with venetoclax in patients with relapsed/refractory or previously untreated B-cell NHL
- To confirm exposure to cyclophosphamide, doxorubicin, and vincristine when given in combination with rituximab, obinutuzumab, and/or venetoclax

Secondary Efficacy Objectives

The secondary efficacy objectives of this study include the following:

- To make a preliminary assessment of efficacy when venetoclax and R-CHOP are administered in combination to patients with previously untreated DLBCL, as measured by:
 - Objective response (OR) rate
 - CR rate as determined by CT scan
 - Duration of response (*DOR*)
 - Progression-free survival (PFS)
- *12 month PFS estimate*
- Overall survival (OS)
- To make a preliminary assessment of efficacy when venetoclax and G-CHOP are administered in combination, as measured by OR rate, CR rate, and PFS.

Exploratory Objectives

The exploratory objectives of this study are the following:

- To make a preliminary assessment of potential biomarkers that might predict disease response or resistance to treatment with the venetoclax plus R-CHOP or G-CHOP combinations in the relapsed or previously untreated setting:
 - Bcl-2 and Bcl-2 family protein expression, including Bcl-xl and Mcl-1, by immunohistochemistry (IHC)
 - BCL2* and c-MYC copy number gain by fluorescence in situ hybridization (FISH) and translocation t(14;18) by FISH
 - Expression of transcripts for Bcl-2 family members, other apoptotic genes, and genes associated with ABC or GCB subtypes of DLBCL
 - Subgroups relevant to DLBCL biology that are defined genetically or by poor prognosis, including CD79b, Myd88, CARD11, TNFAIP3, epigenetic markers, and MYC translocation
- To make a preliminary assessment of the efficacy of venetoclax and R-CHOP in different potential prognostic subgroups, including DLBCL genotypic subtypes (e.g., ABC; GCB), high Bcl-2 (Bcl-2-positive) expression, as well as patients displaying *BCL2* and MYC translocations (Double Hit)
- To make a preliminary assessment of minimal residual disease (MRD) as a prognostic marker in DLBCL
- To evaluate the prognostic significance of interim PET assessment in this setting

Study Design

Description of Study

This is a Phase Ib/II, multicenter, open-label, dose-finding study of venetoclax administered orally in combination with rituximab or obinutuzumab and standard doses of CHOP in patients

with NHL. The study will consist of two stages: a dose-finding Phase Ib stage and a Phase II expansion stage. In the Phase I portion of the study, two parallel treatment arms will explore doses of venetoclax ranging from 200 to 800 mg administered in combination with R-CHOP and G-CHOP. Patients will be treated for a total of eight cycles (six cycles of CHOP and eight cycles of venetoclax + rituximab or venetoclax + obinutuzumab). Each cycle will consist of 21 days. Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor. The maximum tolerated dose (MTD) of venetoclax in combination with R-CHOP and G-CHOP will be determined separately for each arm during the dose-finding stage.

The dose and dose schedule for venetoclax for each arm determined in Phase I will be used in the Phase II expansion stage for that arm.

For the Phase II portion of the study, the venetoclax dose for Arm A is 800 mg on a non-continuous dosing schedule of Cycle 1 Days 4–10 and Cycles 2–8 Days 1–10, as determined by the Phase Ib portion of the study based on safety and tolerability observed in patients treated in the dose escalation portion of the study.

If there are concerns about the tolerability of the Phase II dose at any time during the Phase II study, a lower dose or an alternative dosing schedule for venetoclax + R-CHOP or G-CHOP may be explored on a case by case basis based on the guideline.

For the Phase II R-CHOP arm of the study, after the first 20 patients have completed Cycles 1 and 2 of study treatment, the Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC) will meet to review safety data for all patients treated in both the Phase Ib and Phase II portions of the study in order to confirm the safety and tolerability of the combination therapy at the venetoclax dose chosen at the end of Phase Ib. Enrollment will continue while the interim safety analysis is being conducted.

On the basis of this review, changes may be made to the dose or the dosing schedule of the Phase II.

Number of Patients

The study will enroll approximately 24–60 patients during the dose-finding stage and approximately 180–200 patients in the Phase II portion at approximately 69 investigative sites in North America, the European Union, and Asia Pacific.

Target Population: Inclusions Criteria

Patients must meet the following criteria for study entry:

Patients enrolled in the Dose Finding Portion of the Study:

- Patients must have histologically confirmed B-cell NHL (and have never received previous R-CHOP treatment), except mantle cell lymphoma (MCL) or small lymphocytic lymphoma (SLL), in order to enroll in this portion of the study
- Any relapsed/refractory patients that are enrolled during the dose escalation should have received only a single previous treatment regimen

Patients Enrolled in the Phase II Portion of the Study:

- Patients must have previously untreated CD20-positive DLBCL and International Prognostic Index (IPI) score must be 2–5 in order to enroll in this portion of the study.

All Patients

- Signed informed consent form(s)
- At least one bi-dimensionally measurable *lymphoma* lesion on CT scan defined as > 1.5 cm in its longest dimension, *which is also ¹⁸F-fluorodeoxyglucose (FDG) avid by screening PET scan.*
- Ability and willingness to comply with the study protocol procedures
- Age ≥ 18 years
- Confirmed availability of archival or freshly biopsied tumor tissue meeting protocol defined specifications prior to study enrollment

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Adequate hematologic function (unless because of underlying disease, as established by extensive bone marrow involvement or *as a result* of hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator) defined as follows:
 - Hemoglobin ≥ 9 g/dL
 - ANC $\geq 1.5 \times 10^9/L$
 - Platelet count $\geq 75 \times 10^9/L$
- For women who are not postmenopausal (≥ 12 months of non-therapy–induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined non-hormonal contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 12 months after the last dose of rituximab or 18 months after the last dose of obinutuzumab
 - Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception
- Non-vasectomized male patients must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 12 months after completing therapy with rituximab or 18 months after completing therapy with obinutuzumab:
 - A partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration
 - Total abstinence from sexual intercourse; double-barrier method (condom+diaphragm or cervical cup with spermicidal, contraceptive sponge, jellies, or cream)
 - Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Males must agree to abstain from sperm donation for at least 12 months after the last dose of rituximab or 18 months after the last obinutuzumab dose.

Exclusion Criteria

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

Patients enrolled in the Dose-Finding Portion of the Study

- Patients with MCL or SLL histology will be excluded from study entry

Patients Enrolled in the Phase II Portion of the Study

- Patients with transformed lymphoma (*patients with discordant bone marrow involvement(i.e., low grade histology in bone marrow) may be considered after discussion with the Medical Monitor*)
- Prior therapy for NHL

All Patients

- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Contraindication to receive any of the individual components of CHOP, rituximab or obinutuzumab
- Prior anthracycline therapy
- Ongoing corticosteroid use > 30 mg/day of prednisone or equivalent. Patients who received corticosteroid treatment with ≤ 30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to Cycle 1 Day 1. Patients may have received a brief (< 7 days) course of systemic steroids (≤ 100 mg prednisone equivalent per day) prior to initiation of study therapy for control of lymphoma-related symptoms.

- CNS lymphoma or *primary mediastinal DLBCL*
- Vaccination with live vaccines within 28 days prior to treatment
- Chemotherapy or other investigational therapy within 28 days prior to the start of Cycle 1.
- History of other malignancy that could affect compliance with the protocol or interpretation of results
 - Patients with a history of curatively treated basal or squamous cell carcinoma or Stage 1 melanoma of the skin or in situ carcinoma of the cervix are eligible.
 - Patients with a malignancy that has been treated with surgery alone with curative intent will also be excluded, unless the malignancy has been in documented remission without treatment for ≥ 3 years prior to enrollment.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient, including renal disease that would preclude chemotherapy administration or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, congestive heart failure, myocardial infarction within the past 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Left ventricular ejection fraction $< 50\%$ as defined by multiple-gated acquisition (MUGA). Echocardiogram may be used if MUGA is not available.
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1
- Received the following agents within 7 days prior to the first dose of venetoclax:
 - Steroid therapy for anti-neoplastic intent within 7 days prior to *Cycle 1 Day 1*.
 - Strong and moderate CYP3A inhibitors
 - Strong and moderate CYP3A inducers
 - Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within 3 days prior to the first dose of venetoclax.
- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Presence of positive test results for hepatitis B (HBcAb) or hepatitis C (hepatitis C virus [HCV] antibody)
 - Patients who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation
 - Patients with occult or prior hepatitis B virus (HBV) infection (defined as positive total HBcAb and negative hepatitis B surface antigen [HBsAg]) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing.
- Known infection with HIV or human T-cell leukemia virus 1
- Women who are pregnant or lactating
- Recent major surgery (within 6 weeks prior to the start of Cycle 1 Day 1), other than for diagnosis
- Any of the following abnormal laboratory values:
 - Calculated estimated creatinine clearance (CRCL) < 50 mL/min with the use of the 24-hour creatinine clearance or modified Cockcroft-Gault equation (with the use of ideal body mass [IBM] instead of mass):

$$\text{CRCL} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [0.85 \text{ if female}]}{72 \cdot \text{serum creatinine (mg/dL)}}$$

Or, if serum creatinine is in $\mu\text{mol/L}$:

$$\text{CRCL} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine } (\mu\text{mol/L})}$$

AST or ALT $> 2.5 \times \text{ULN}$ (*unless due to disease involvement; Medical Monitor to be consulted prior to enrollment*)

Total bilirubin $\geq 1.5 \times \text{ULN}$ (or $> 3 \times \text{ULN}$ for patients with documented Gilbert syndrome)

INR $> 1.5 \times \text{ULN}$ for patients not receiving therapeutic anticoagulation

PTT or aPTT $> 1.5 \times \text{ULN}$

Length of Study

The length of study will be the time from screening of the first patient through 2 years following completion of study treatment of the last patients enrolled. This time is expected to be approximately 60 months.

End of Study

The end of study will be defined as 2 years following completion of treatment of the last patient enrolled.

Outcome Measures

Efficacy Outcome Measures

The following activity outcome measures will be assessed:

- Primary outcome measures:
 - CR, as defined by PET-CT scan as well as bone marrow examination when applicable
- Secondary outcome measures:
 - CR, as defined by CT scan and bone marrow examination, when applicable
 - OR, defined as a PR or CR
 - DOR, defined as the first occurrence of a documented response until the time of relapse or death from any cause
 - PFS, defined as the time from date of first dose of study drug to the first occurrence of progression, relapse, or death while in the study, where death while in the study is defined as death from any cause within 12 weeks of the last tumor assessment
 - PFS at 12 months
 - Relative dose intensity
 - OS, defined as the time from date of first dose of study drug until the date of death from any cause. For patients who have not died, survival data will be censored at the date of last contact.

OR and disease progression will be determined with use of the modified Lugano Classification: Revised Criteria for Response Assessment.

Safety Outcome Measures

The safety and tolerability of the combination of venetoclax plus R-CHOP or G-CHOP will be assessed using the following primary safety outcome measure:

- Incidence and nature of combination dose-limiting toxicity (DLTs)

In addition, safety will be assessed using the following secondary safety outcome measures:

- Incidence, nature, and severity of adverse events and serious adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Adverse events of special interest include Grade 4 neutropenic fever, Grade ≥ 3 infusion-related reactions (IRR) to rituximab or obinutuzumab, and Grade ≥ 4 tumor lysis syndrome (TLS).
- Change in clinical laboratory results (including hematology and chemistry) and vital signs
- Maintenance of relative dose intensity of CHOP chemotherapy

Pharmacokinetic Outcome Measures

The following PK parameters will be derived from the plasma concentration-time profile of prednisone, venetoclax, and relevant metabolites following administration when appropriate, as data allow:

- Total plasma exposure (AUC)
- Time to maximum observed plasma concentration (t_{max})
- Maximum plasma concentration observed in plasma (C_{max})
- Minimum plasma concentration under steady-state conditions within a dosing interval (C_{min}) in plasma

The following PK parameters will be determined from the concentration-time profiles of rituximab, obinutuzumab, and cyclophosphamide, vincristine, and doxorubicin (CHO) components, as applicable:

- C_{max} in serum or plasma, as appropriate
- C_{min} in serum or plasma, as appropriate

Other PK parameters such as clearance, volume of distribution (V), and half-life may also be calculated as data allow.

Exploratory Outcome Measures

The following correlative biology measures will be assessed:

- Bcl-2 high (Bcl-2 positive) as defined by IHC and Bcl-2 family protein expression by immunohistochemistry (IHC)
- *BCL2* and c-MYC copy number gain by FISH and translocation t(14;18) by FISH
- Expression of transcripts for Bcl-2 family members, other apoptotic genes, and genes associated with the activated B cell-like (ABC) or germinal center B cell-like (GCB) subtypes of DLBCL
- Subgroups relevant to DLBCL biology, including CD79b, Myd88, CARD11, TNFAIP3, epigenetic markers, and MYC translocation

Investigational Medicinal Products

The Investigational Medicinal Products used in this study are venetoclax, rituximab, and obinutuzumab (GA101).

Venetoclax

The venetoclax tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Each bottle will be labeled per local regulatory requirements. A desiccant canister may be included in the bottle. The tablets must be stored at 15°C–25°C (59°F–77°F). If supplied with a desiccant, the desiccant canister should be returned to the bottle directly after each tablet removal.

Study patients will self-administer venetoclax tablets by mouth once daily (QD). Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or the patient's first meal of the day. *A meal containing approximately 30% of the total caloric content from fat is recommended to ensure adequate absorption of*

venetoclax. On days that pre-dose PK sampling is required, *the patient's first meal of the day (e.g., breakfast) will be consumed in the morning at the clinic, and venetoclax dosing will occur in the clinic after completion the meal-to facilitate PK sampling.*

On days when venetoclax plus R-CHOP or G-CHOP are given, the order of study treatment administration will be venetoclax prior to rituximab or obinutuzumab, and rituximab or obinutuzumab prior to CHOP (with the exception of the first dose of prednisone in each cycle). On days when both venetoclax and prednisone are given, venetoclax will be taken prior to prednisone. If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be given and the second dose noted in the drug log. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible and ensure that the minimal interval between the current dose and the next dose is at least 16 hours in order to avoid excessive drug accumulation after the next dose. Patients will be instructed to record the date and time they take their daily dose of venetoclax and prednisone. Diaries will be provided by the Sponsor for this purpose. Venetoclax must be stored according to labeled storage conditions.

All patients must receive prophylaxis for TLS prior to the initiation of venetoclax plus R-CHOP or G-CHOP study treatment.

Rituximab

Rituximab (Rituxan[®]/MabThera[®]) is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/mL in 100-mg (10 mL) and 500-mg (50 mL) single-use vials. The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, and 0.7 mg/mL polysorbate 80, after reconstitution with Sterile Water for Injection. The pH is adjusted to 6.5. Vials are for single use. Each vial and carton will contain a label (either single-panel or booklet) affixed to the vial or carton per individual country requirements.

Rituximab will be administered intravenously once per 21-day cycle in combination with CHOP for up to six cycles and as a single agent for two additional cycles. Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor. The infusion of 375 mg/m² will be based on the patient's body surface area (BSA) at screening and will remain the same throughout the study unless there is a > 10% change in body weight. On a given day, rituximab should be given after venetoclax and prior to CHOP (with the exception of the first dose of prednisone in each cycle).

Rituximab should not be administered as an IV push or bolus. IRRs may occur. Premedication consisting of acetaminophen, diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered beginning with the first infusion. Premedication may attenuate IRRs. Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

There will be no rituximab dose modification in this study. Patients who are at high risk for IRR or TLS complications may, at the investigator's discretion, receive their initial dose of rituximab split over 2 consecutive days (e.g., 125 mg/m² on Cycle 1 Day 1, 250 mg/m² on Cycle 1 Day 2). If the patient tolerates the first infusion well, subsequent rituximab infusions may be administered at an initial rate of 100 mg/hr and increased in 100-mg/hr increments at 30-minute intervals to a maximum of 400 mg/hr, as tolerated or per an institution's standard of care IV administration procedure.

Any NCI CTCAE v4.0 toxicity Grade ≥ 3 in severity that is deemed related to rituximab treatment will require interruption of study treatment until resolution to Grade ≤ 1 . Resumption of rituximab treatment may be considered in patients with resolution of toxicities to Grade ≤ 2 within 3 weeks at the discretion of the investigator after consultation with the study Medical Monitor. Failure of such toxicities to resolve after 3 weeks of suspended study treatment will require permanent discontinuation of rituximab.

Patients who discontinue rituximab because of rituximab-related toxicity may continue to receive CHOP and/or venetoclax only after consultation by the investigator with the Medical Monitor.

Obinutuzumab

Obinutuzumab is provided as a single-dose, sterile liquid formulation in a 50 mL pharmaceutical-grade glass vial containing a nominal 1000 mg of obinutuzumab (G3 material). The formulated drug product consists of 25 mg/mL drug substance (G3) formulated in histidine, trehalose, and poloxamer 188. The vial contains 41 mL (with 2.5% overfill).

The recommended storage conditions for the obinutuzumab drug product are between 2°C and 8°C and protect from light. Chemical and physical in-use stability for obinutuzumab dilutions in 0.9% sodium chloride (NaCl) has been demonstrated for 24 hours at 2°C–8°C and at ambient temperature and ambient room lighting. The prepared diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C. Obinutuzumab should not be frozen or shaken. Mix gently. All transfer procedures require strict compliance with aseptic techniques. Do not use an additional in-line filter; this will avoid potential adsorption.

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg in combination with CHOP for up to six cycles and as a single agent for two additional cycles. Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor. On a given day, obinutuzumab should be given after venetoclax and prior to CHOP (with the exception of the first dose of prednisone in each cycle), and patients should be observed for 30 minutes prior to starting CHOP. Patients at high risk for IRR or TLS complications may, at the investigator's discretion, receive their obinutuzumab dose split over 2 consecutive days (e.g., 100 mg on Day 1, 900 mg on Day 2). During Cycle 1, obinutuzumab will also be administered on Days 8 and 15.

Non-Investigational Medicinal Products

CHOP Chemotherapy

CHOP chemotherapy consists of IV cyclophosphamide, IV doxorubicin, vincristine administered by IV push, and oral prednisone or prednisolone. Standard CHOP will be administered for six 21-day cycles. Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor.

- Cyclophosphamide 750 mg/m² administered intravenously on Day 1
- Doxorubicin 50 mg/m² administered intravenously on Day 1
- Vincristine 1.4 mg/m² administered by IV push on Day 1 with a cap of 2.0 mg
- Prednisone 100 mg/day orally (PO) on Days 1–5

Permitted Concomitant Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening through 30 days after the last dose of venetoclax or CHOP, or 90 days after the last dose of rituximab or obinutuzumab, whichever is later. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who are receiving oral contraceptives, stable doses of hormone replacement therapy, or other maintenance therapy should continue their use.

Steroid use not otherwise dictated by the protocol CHOP treatment will follow the guidelines outlined below:

- Corticosteroid use > 30 mg/day of prednisone or equivalent: Not allowed within 7 days prior to *Cycle 1 Day 1* except as specified below
- Corticosteroid use 15–30 mg/day of prednisone or equivalent: Must be documented to be on a stable dose of at least 4 weeks' duration prior to first dose of study drug.
- Corticosteroid use < 15 mg/day of prednisone or equivalent: Allowed

Exceptions to the above guidelines:

- Corticosteroid used for malignancy-related symptom control (up to 100 mg/day of prednisone or equivalent) prior to initiation of study treatment. Once study treatment has been given, corticosteroid use may be tapered down (must be \leq pre-study treatment dose) for no more than 5 days.
- Premedication for rituximab or obinutuzumab infusions, as indicated per protocol and/or site local practice (may replace dose of CHOP prednisone)
- Inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease
- Topical steroids
- Replacement corticosteroid therapy for an inherited or acquired deficiency
- Steroid use to treat emergent issues not related to anti-neoplastic intent is allowed for no more than 7 days per event. For steroid treatment > 7 days, the Medical Monitor must be consulted to discuss allowing the patient to continue treatment.

Excluded Therapy

Patients who are discontinued from study treatment will be followed for safety outcomes for 30 days following the patient's last dose of venetoclax or CHOP (or 90 days following the patient's last dose of rituximab or obinutuzumab, whichever is later) or until the patient receives another anti-cancer therapy, whichever occurs first.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy. Supplemental systemic therapy for prophylaxis of CNS disease is permitted according to institutional practice only after primary response assessment and must be recorded in the eCRF.
- Radiotherapy prior to primary response assessment
- Immunotherapy
- Hormone therapy (other than contraceptives, hormone replacement therapy, or megestrol acetate)
- Any therapies intended for the treatment of lymphoma/leukemia whether U.S. Food and Drug Administration (FDA) approved or experimental (outside of this study)
- Warfarin may be co-administered with venetoclax with caution and with the guidance of the Medical Monitor.

The following concomitant medications are not allowed from 7 days prior to the first dose of study drug and during venetoclax administration:

- Corticosteroid use > 30 mg/day of prednisone or equivalent (with some exceptions).
- Strong and moderate CYP3A4 inducers

The following concomitant medications are not allowed from 7 days prior to the administration of the first dose of study drug:

- Strong and moderate CYP3A inhibitors
- Strong and Moderate CYP3A inducers

Exclude strong and moderate CYP3A inhibitors through the DLT assessment period and consider alternative medications. If a patient requires use of these medications while he or she is receiving the target dose of venetoclax, once the DLT assessment period is complete, use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration.

After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.

- Exclude strong and moderate CYP3A inducers through the DLT assessment period and consider alternative medications. If a patient requires use of these medications while he or she is receiving the target dose of venetoclax, once the DLT assessment is complete, use with caution and contact the Medical Monitor for guidance.

Statistical Methods

Primary Analysis

The final analysis will be based on patient data collected through study discontinuation. Analyses will be based on treated patients (i.e., patients who have received any amount of R/G-CHOP or venetoclax). Analyses will be provided separately for the dose-finding and extension cohorts where appropriate. Data from patients who receive R-CHOP or G-CHOP only (i.e., have not received any venetoclax), will be summarized separately.

Determination of Sample Size

The sample size for the dose-finding stage is based on a modified 3+3 design in order to guide dose and schedule selection for the Phase II portion on the basis of DLTs. The expected enrollment for the dose-finding stage is 3–6 patients per dose level in each of the R-CHOP+venetoclax and G-CHOP+venetoclax arms.

The sample size for the R-CHOP+venetoclax arm in Phase II is based on obtaining a sufficient number for estimation of PET-negative CR rate in patients with *DE* (Bcl-2 and c-Myc co-expressing) DLBCL, overall, for Bcl-2 high patients, and within each of four mutually exclusive biological subgroups: Bcl-2 high and ABC, Bcl-2 high and GCB, Bcl-2 low and ABC, and Bcl-2 low and GCB. The expected enrollment for the R-CHOP+venetoclax arm in Phase II is approximately 160–200 patients in order to enroll approximately 50 *DE*-DLBCL patients, approximately 80–100 Bcl-2 high patients, and approximately 40–50 patients in each of the two Bcl-2 high subgroups. With 50 patients, 95% confidence intervals for estimation of CR would have a margin of error not exceeding 16%. The margin of error would decrease to 9% with 150 patients and to 8% with 200 patients

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABC	activated B cell-like
ADCC	antibody-dependent cell-mediated cytotoxicity
AUC	area under the concentration-time curve
AUC ₀₋₂₄	area under the concentration-time curve from time 0 to time 24 hours
ALL	acute lymphoblastic leukemia
anti-HBc	anti-hepatitis B core antibody
BR	bendamustine and rituximab
BSA	body surface area
CLL	chronic lymphocytic leukemia
C _{max}	maximum concentration observed in serum or plasma, as appropriate
C _{min}	minimum concentration under steady-state conditions within a dosing interval in serum or plasma
CHO	cyclophosphamide, vincristine, and doxorubicin
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CR	complete response
CRCL	creatinine clearance
CRi	incomplete marrow recovery
CT	computed tomography
CV	cardiovascular
<i>DE</i>	<i>double expressor</i>
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
FDG	¹⁸ F-fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FL	follicular lymphoma
G	obinutuzumab (GA101)
GCB	germinal center B cell-like
G-CHOP	obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor

Abbreviation	Definition
GI	gastrointestinal
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HD	high dose
HIPAA	U.S. Health Insurance Portability and Accountability Act
IBM	ideal body mass
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
IL	interleukin
IMC	Internal Monitoring Committee
IND	Investigational New Drug
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	intravenous
IxRS	interactive voice/ Web response system
JC	John Cunningham
Ki	dissociation constant
LD	low dose
LDi	longest transverse diameter of a lesion
MCL	mantle cell lymphoma
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NaCl	sodium chloride
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NK	natural killer
OS	overall survival
OR	objective response
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography

Abbreviation	Definition
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	orally
PR	partial response
PVC	polyvinylchloride
QD	once daily
R	rituximab
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RCR	Roche Clinical Repository
SC	subcutaneous
SLL	small lymphocytic lymphoma
SOC	Scientific Oversight Committee
SPD	sum of the product of the diameters
TLS	tumor lysis syndrome
TMA	tissue microarray
t_{\max}	time to maximum observed plasma concentration
ULN	upper limit of normal
V	volume of distribution

1. **BACKGROUND**

1.1 **BACKGROUND ON DISEASE**

1.1.1 **Indolent Non-Hodgkin's Lymphoma**

Non-Hodgkin's lymphoma (NHL) is the most common hematologic malignancy in adults. It is estimated that in 2010 there were 93,172 new cases of NHL in Europe and 65,540 new cases of NHL in the United States ([GLOBOCAN 2008](#); [American Cancer Society 2010](#)). The majority of NHLs (also known as malignant lymphoma) is of B-cell origin and characterized by the expression of a membrane antigen, CD20, that is important in cell cycle initiation and differentiation. NHL can be divided into aggressive and indolent NHL. Indolent NHLs are a heterogeneous group of malignant lymphomas and account for about one-third of all NHLs. Follicular lymphoma (FL) is the most common subtype of indolent NHL in the Western hemisphere and is associated with follicle center B cells that typically contain the *BCL2* chromosome translocation t(14:18) that leads to overexpression of the intracellular anti-apoptotic protein Bcl-2. Although FL is the most common subtype of indolent NHL, there are also several histological non-follicular subtypes including marginal zone lymphoma, Waldenström's macroglobulinemia (also known as lymphoplasmacytic lymphoma), and small lymphocytic lymphoma (SLL). Early-stage indolent NHL may be effectively treated with radiation therapy, but advanced stages remain incurable.

The clinical course of indolent NHL is characterized by remission and relapse. Although there is no agreed-upon standard therapy for indolent NHL, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is a common regimen that results in high response rates and long remission duration in many patients, particularly in those patients with FL ([Czuczman et al. 1999](#)). The disease initially responds to radiation and/or immunochemotherapy with conventional agents, but patients eventually suffer multiple relapses distinguished by increasing refractoriness and decreasing duration of response (DOR) in subsequent lines of therapy. Patients with advanced stage disease are not considered curable with conventional treatment and ultimately die from recurrent disease or treatment-related toxicity. Therefore, there is a need for the development of new treatments that could improve both response and survival rates of patients with indolent NHL.

1.1.2 **Diffuse Large B-Cell Lymphoma**

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, comprising approximately 30% of all NHL cases. Approximately 75% of patients with DLBCL who are treated with current standard R-CHOP therapy achieve a complete remission, and 50%–60% of patients are cured of their disease with this treatment.

Although there is currently no way to prospectively identify individual patients who will be cured, clinical factors are used to define prognostic risk groups associated with predictive outcomes. The International Prognostic Index (IPI) is a prognostic tool that uses five clinical factors to predict outcome of patients with aggressive NHL. The IPI

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

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

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

Bcl-2 is an anti-apoptotic molecule overexpressed in many hematologic malignancies including many DLBCLs, either through translocation of the *BCL2* gene in juxtaposition with the IGH gene t(14;18), through gene amplification, or by other mechanisms (Gascoyne et al. 1997; Davis et al. 2001). Bcl-2 protein inhibits death of lymphoma cells in response to chemotherapy and other anti-neoplastic agents including rituximab (R). Overexpression of *BCL2* has been shown to be associated with inferior outcomes in DLBCL with standard treatment (Iqbal et al. 2011; Hu et al. 2013; Visco et al. 2013). The frequent overexpression of *BCL2* combined with its contribution to therapy resistance makes *BCL2* inhibition an attractive therapeutic target in DLBCL.

DLBCL is a molecularly heterogeneous disease with different molecular subtypes that have been identified with the use of gene expression profiling (Rosenwald et al. 2002). The two major subtypes, germinal center B cell-like (GCB) and activated B cell-like (ABC), show activation of different oncogenic and survival pathways. Furthermore, they are associated with different prognoses, with survival being significantly better in patients with GCB-DLBCL than in those with ABC-DLBCL. Although evidence for a prognostic effect of *BCL2* is greatest in the GCB subtype, both GCB- and ABC-DLBCL overexpress *BCL2* in approximately 50% of cases, arguing for biological relevance of *BCL2* in both subtypes. The implications of *BCL2* inhibition in each subtype are unknown, supporting the need to investigate the activity of *BCL2* inhibition in combination with chemotherapy in each subgroup. Patients with expression of both Bcl-2 and c-Myc proteins (i.e., double *expressor*- [DE-] DLBCL) have been

recently identified as a poor prognostic subgroup, characterized in part by overexpression of *BCL2*, for whom the addition of venetoclax (GDC-0199) might add substantial therapeutic benefit. Patients with (DE-) DLBCL, even in the absence of chromosomal translocation, have an inferior outcome when compared with patients with DLBCL that does not express both proteins, and thus represent a poor-prognosis group in need of effective therapies (Green et al. 2012; Johnson et al. 2012; Hu et al. 2013; Valera et al. 2013). Since *BCL2* expression contributes to the pathogenesis of some types of lymphoid malignancies, including DLBCL, the inhibition of *BCL2* function with venetoclax could restore the sensitivity of tumor cells to the current standard therapy, R-CHOP, and therefore could provide an effective new therapy for this group with a high, unmet medical need.

Patients with chromosomal translocations in *BCL2* and *MYC* (i.e. Double Hit) have also been identified as a poor prognostic subgroup (Savage et al. 2009; Barrans et al. 2010) and also comprise a subgroup of patients with an unmet medical need.

1.2 BACKGROUND ON THE MOLECULES

1.2.1 Bcl-2 Protein Family

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The *BCL2* oncogene was first identified in FL where the t(14;18) chromosomal translocation results in significant overexpression of the protein in B cells. The *BCL2* family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four *BCL2* homology domains (Cory and Adams 2002; Borner 2003; Cory et al. 2003). *BCL2* overexpression is a major contributor to the pathogenesis of many types of lymphoid malignancies and has been implicated as a cause of chemotherapy resistance.

1.2.2 Venetoclax

1.2.2.1 Venetoclax Nonclinical Activity and Pharmacokinetic Profile

Venetoclax (synonymous with GDC-0199 and ABT-199; venetoclax will be used throughout the protocol) is a highly selective, orally available small molecule Bcl-2 family protein inhibitor that binds with high affinity (dissociation constant $[K_i] < 0.10$ nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-X_L and Bcl-w (>480-fold and >2000-fold lower affinity than to Bcl-2, respectively). Overexpression of anti-apoptotic Bcl-2 family proteins is associated with resistance to chemotherapy and antagonism of the action of these proteins might overcome resistance and enhance response to therapy. Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for anti-tumor therapy.

In vitro, venetoclax has demonstrated broad cell-killing activity against a panel of lymphoma and leukemia cells including B-cell FL, mantle cell lymphoma (MCL), DLBCL, and acute myeloid leukemia. Venetoclax was especially potent against cell lines

expressing high levels of Bcl-2. Leukemia and lymphoma cell lines bearing the t(14;18) translocation were significantly more sensitive to venetoclax than were wild-type cell lines.

Venetoclax inhibited subcutaneous (SC) murine xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia (ALL) and NHL.

The pharmacokinetic (PK) profile of venetoclax was evaluated in multiple animal species. In mice, rats, monkeys, and dogs, low plasma clearance and low volumes of distribution characterized the venetoclax PK profile. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs. Food had a marked effect on the oral bioavailability in dogs, with a 30%–50% higher plasma concentration compared with fasted animals.

Venetoclax demonstrated high protein binding to human, rat, dog, and monkey plasma proteins (>99.9%). In rats, venetoclax was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat but was poorly distributed in testes, brain, muscle, and bone. Liver metabolism was the major route of elimination, with biliary excretion of the parent drug playing the secondary role in rats. Venetoclax showed moderate metabolic stability in in vitro hepatic systems across species tested, except for low to moderate stability in dog hepatocytes.

In vitro, venetoclax was metabolized by CYP3A4; thus, co-administration of venetoclax with drugs that inhibit CYP3A4, is predicted to cause a significant increase in the exposure of venetoclax. Venetoclax is a substrate for P-gp and BCRP. Active uptake of venetoclax was not observed in cells overexpressing OATP1B1, OATP1B3, or OCT1 indicating that venetoclax is not a substrate for those transporters in vitro.

On the basis of in vitro results, venetoclax was a P-gp, BCRP, and OATP1B1 inhibitor. It was not a potent in vitro inhibitor of CYP3A4, CYP1A2, CYP2B6, or CYP2D6 ($IC_{50} > 30 \mu\text{M}$); and it did not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM . Venetoclax is also not predicted to cause inhibition of CYP2C19, CYP2C8, CYP2C9, and UGT1A1 at clinically relevant concentrations. It is not an inhibitor of UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

A more detailed discussion of the nonclinical activity of venetoclax including pharmacokinetics and metabolism can be found in the ABT-199/GDC-0199 Investigator's Brochure.

1.2.2.2 Venetoclax Nonclinical Toxicology

Toxicology assessments completed to date with venetoclax are general toxicology studies with periods of once-daily oral dosing ranging from 2 weeks to 6 months in mice, from 2 weeks to 13 weeks in rats, and from 1 week to 9 weeks in dogs; in vitro and in vivo genetic toxicology; embryo-fetal development in female mice and rabbits; and fertility and early embryonic development in male and female mice. The maximum

steady state venetoclax plasma exposures (mean area under the concentration-time curve [AUC]) achieved in the IND-enabling 4 week studies were 92 $\mu\text{g}\cdot\text{h/mL}$ (at 600 mg/kg/day) in mice and 572 $\mu\text{g}\cdot\text{h/mL}$ (at 150 mg/kg/day) in dogs. In the chronic toxicity studies, AUCs reached 34.1 $\mu\text{g}\cdot\text{h/mL}$ (at 300 mg/kg/day) in mice and 86 $\mu\text{g}\cdot\text{h/mL}$ (at 20 mg/kg/day) in dogs. In rats, exposures were higher in females than in males; at dosages of 150 and 400 mg/kg/day in the 13 week maximum tolerated dose study, exposures ranged up to 83.1–127.8 $\mu\text{g}\cdot\text{h/mL}$ in females and up to 26.4–44.2 $\mu\text{g}\cdot\text{h/mL}$ in males.

The primary toxicities associated with venetoclax administration included effects on the hematologic system (decreased lymphocytes and erythrocytes) in mice, rats, and dogs; the male dog reproductive system (testicular germ cell depletion); and embryo-fetal toxicity in mice.

In mice, rats, and dogs, venetoclax produced generally dose-related decreases in lymphocytes in the peripheral blood (of up to 75% in mice, up to 64% in rats, and up to 81% in dogs) and in lymphoid tissues. In dogs, the recovery of lymphocyte counts (total lymphocytes, CD4 + and CD8 + T cells and mature B cells) was prolonged, requiring up to 18 weeks after completion of 2 weeks of dosing. B cells were the most sensitive lymphocyte subtype based on the magnitude of decrease and/or the length of time required for recovery (i.e., 25%–111% of individual baseline; mean reversal to 54% of baseline average). T-cell subsets reversed more readily and showed more dose-dependence in recovery time and extent. Decreases of lymphocytes in lymphoid tissues were reversible in mice and reversible to partially reversible in dogs. Venetoclax-related decreases in lymphocytes in blood and lymphoid tissues are considered pharmacologically-mediated and non-adverse (Marsden and Strasser, 2003).

In the 4 week mouse and dog studies, dose-related reversible decreases in RBC mass were observed. Effects on RBC mass were typified by hemoglobin decreases. At the highest dosages administered, decreases in hemoglobin reached -21% in mice at 600 mg/kg/day and -23% in dogs at 150 mg/kg/day, and were considered to be adverse based on a criterion of -20% decrease. In rats, decreases in hemoglobin were more severe than in mice and dogs at comparable exposures and reached 30% to 49% at ≥ 150 mg/kg/day in females. Hematologic parameters (lymphocyte counts and RBC mass) are readily monitored in clinical trial subjects.

In dogs, venetoclax produced adverse, non-reversible, non-dose-related microscopic findings of testicular germ cell depletion at all dosages tested; there were no testicular effects in mice. The translatability of the testicular findings in dogs to humans is unknown, but this change may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis (Olderied et al. 2001; Sugiyama et al. 2001; Yan et al. 2003). No effects of venetoclax have been identified in female reproductive tissues in mice or dogs in general toxicology studies.

Venetoclax resulted in increased post-implantation loss and decreased fetal body weights in the mouse embryo-fetal development study at the highest dosage administered (150 mg/kg/day); the no-observed-adverse-effect level was defined at the mid-dose of 50 mg/kg/day. Venetoclax was not teratogenic, and there were no other effects on development or fertility.

Additional noteworthy effects of venetoclax included white hair coat discoloration in dogs (occurring after approximately 3 months of dosing in the 9 month study) and single cell necrosis in various epithelial tissues (gallbladder, exocrine pancreas, stomach, exocrine pancreas, and epididymides) in dogs. Single cell necrosis was minimal except for non-dose-dependent minimal to mild single cell necrosis in the pylorus of the stomach at ≥ 2 mg/kg/day in the 9 month study. After 4 weeks of dosing and a 4 week recovery period, reversibility was observed in the gallbladder and exocrine pancreas, but minimal single cell necrosis was still present in the epididymides and prostate (potentially related to the testicular effects) and in the stomach. Single cell necrosis was considered not to be adverse due to its minimal to mild magnitude and because no loss of mucosal integrity was observed histopathologically. The hair coat change correlated histopathologically with decreased pigment in hair follicle bulbs, and is consistent with the pharmacologic inhibition of Bcl-2 by venetoclax, leading to Bcl-2 functional loss in hair follicle melanocytes dependent on Bcl-2 for survival (Yamamura et al. 1996). A dedicated physical examination of the skin and extensive ophthalmic examinations determined that pigmentation of the skin and in the eye (particularly, the iris and fundus) of the dog appeared unaffected. This was confirmed by the absence of associated histopathologic findings in skin (other than in hair follicles) and in the eye. Consequently, white hair coat discoloration was considered non-adverse; reversibility has not been assessed.

Minor effects of venetoclax were: mild, dose-related, transient post-dose emesis, increased salivation, and fecal alterations (unformed or watery feces); minimally increased pigment in Kupffer cells and macrophages in the liver and gallbladder, respectively; and clinical signs of skin swelling, all in dogs. With regard to the latter finding, dogs at the high dosage of 150 mg/kg/day in the 4 week study had clinical signs of swelling of the skin on the ears, head (cranial area), and forepaws and/or hindpaws. Most but not all animals (8 of 10 dogs) were affected, and in three dogs the swelling reaction was observed after the first dose. The clinical signs were transient and sporadic in occurrence, and were absent during the recovery period. A mechanistic basis for the swelling reactions was not established, but the clinical signs were mild to moderate in severity and reversible, and there were no signs of anaphylaxis.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax, nor was there evidence of phototoxicity.

Venetoclax was tested in a battery of safety pharmacology assays, and produced no effects in the CNS/neurobehavioral or respiratory studies in mice at oral doses up to

and including the highest oral dose of 600 mg/kg. No effects on QTc were observed up to a maximum plasma concentration of 46 µg/mL in dogs. In conscious dogs, venetoclax did not produce any cardiovascular effects up to and including the highest oral dose of 150 mg/kg (maximum concentration observed [C_{max}] =16 µg/mL). In the anesthetized dog at higher plasma concentrations, venetoclax produced mild reductions in myocardial contractility (-6% to -13%) and cardiac output (-11% to -19%) at plasma concentrations of ≥16 µg/mL and ≥32 µg/mL, respectively. These concentrations are greater than the plasma concentration of venetoclax in humans (average C_{max} =6.09 µg/mL at the 1200 mg/day dose).

See the ABT-199/Venetoclax Investigator's Brochure for details of the nonclinical studies.

1.2.2.3 Venetoclax Clinical Experience

As of 30 June 2013, a total of 137 patients were dosed with venetoclax in AbbVie and Genentech/Roche oncology studies. Doses administered in venetoclax clinical studies have ranged from 20 to 1200 mg.

The first-in-human venetoclax monotherapy dose-escalation study (Study M12-175) is ongoing in patients with relapsed or refractory chronic lymphocytic leukemia (CLL)/SLL and NHL. Study M13-365 (venetoclax and rituximab administered in combination to patients with relapsed or refractory CLL), Study M12-630 (venetoclax administered in combination with bendamustine and rituximab [BR] to patients with relapsed/refractory NHL), and Study GP28331 (venetoclax administered in combination with obinutuzumab to patients with relapsed or refractory CLL) are also ongoing.

Study M12-175 includes patients with relapsed/refractory CLL/SLL (treatment Arm A) or NHL (treatment Arm B). Patients receive daily dosing until progressive disease (PD) or unacceptable toxicity.

Study M13-365 includes patients with relapsed/refractory CLL. Patients receive venetoclax starting at 50 mg/day, and the dose is escalated to the target cohort dose of venetoclax over 3 weeks, followed by continual daily dosing of venetoclax at the target cohort dose until disease progression. Rituximab is administered starting on Week 4 Day 1 at 375 mg/m² followed by subsequent administrations of 500 mg/m² rituximab on Day 1 of Weeks 5, 6, 10, 14, 18, 22, and 26.

Study M12-630 is a study of venetoclax administered in combination with BR to patients with relapsed /refractory NHL. Patients receive venetoclax starting at 50 mg/day for 3 days with each 28-day cycle of BR, continuing for 6 cycles. Venetoclax dose and duration per cycle are escalated in consecutive cohorts.

Study GP28331 includes patients with relapsed/refractory CLL. Patients receive venetoclax doses that are escalated to the target dose before obinutuzumab treatment is

initiated. Obinutuzumab is administered at a dose of 1000 mg, with the first dose split over 2 days.

Preliminary safety, PK, and efficacy data are summarized below on the basis of data cutoff dates of 11 January 2013 for safety listings.

Dose-limiting toxicity (DLT) assessments are available for patients enrolled in Study M12-175 (through Cohort 8 with a target venetoclax dose of 1200 mg), Study M13-365 (through Cohort 3 with a target venetoclax dose of 400 mg), and Study M12-630 (through Cohort 2 with a target venetoclax dose of 100 mg for 3 days with each cycle of BR).

Seven DLTs of tumor lysis syndrome (TLS) and two DLTs of fatalities in the setting of TLS were reported in the venetoclax clinical program for patients with CLL/SLL (Studies M12-175 and M13-365). Six DLTs of TLS occurred in Study M12-175 at either the starting dose of 100 or 200 mg venetoclax (3 patients in Cohort 1) or the lower lead-in dose of 50 mg venetoclax implemented to minimize the risk of TLS (1 patient each in Cohorts 2 and 4). The sixth DLT of TLS occurred at the maximum designated cohort dose administered in the study (Cohort 8; 1200 mg), and the patient experienced sudden death. In Study M13-365, there was a single DLT of death caused by Grade 5 hyperkalemia in a setting of TLS at the 50-mg lead-in dose. In addition, single non-DLT adverse events of TLS were reported in 1 patient with MCL in Study M12-175 and in 1 patient with CLL in Study M13-365. Events of laboratory TLS were also observed in 2 patients during dosing in Study GP28331 at lead-in doses of 50 mg venetoclax.

In Study GP28331, 4 patients received study treatment; 3 patients received venetoclax for between 3 and 15 days and 1 patient received obinutuzumab and a single dose of venetoclax. All patients discontinued therapy when the study was put on temporary hold after two TLS-related deaths occurred in other clinical studies. In this study, the only reported adverse event related to venetoclax was a serious event of hyperphosphatemia in the setting of laboratory TLS that occurred after the third dose of venetoclax in a patient who had not received obinutuzumab. The event resolved with IV hydration and discontinuation of study therapy.

Two DLTs were reported in patients with NHL treated with venetoclax (Studies M12-175 and M12-630). Both DLTs occurred in Study M12-175 at the 600-mg dose in Cohort 5. This study enrolled a total of 10 patients with a 300-mg lead-in dose and a designated cohort dose of 600 mg. One patient experienced a DLT of serious Grade 3 febrile neutropenia and the other patient experienced a DLT of non-serious Grade 4 neutropenia. Dosing was interrupted and patients were treated with medication; the events resolved and the patients restarted therapy at a reduced dose of 300 mg. No DLTs were reported in Cohort 6 at the designated cohort dose of 800 mg.

Additional DLTs included 1 case each of histiocytosis hematophagic and thrombocytopenia in patients with CLL (both considered related to rituximab rather than venetoclax).

Grade ≥ 3 hematologic toxicity was common in patients with CLL who received venetoclax, but less common in patients with NHL. With single-agent venetoclax in Study M12-175, 37.5% of patients with CLL experienced Grade 3 or 4 neutropenia and 7% experienced Grade 3 or 4 thrombocytopenia, whereas 13% of patients with NHL experienced Grade ≥ 3 neutropenia and 10% experienced Grade ≥ 3 thrombocytopenia. Hematologic toxicity in Study M12-630 (venetoclax in combination with BR in NHL) was not significantly greater than that expected with BR alone.

Data on venetoclax and human pregnancy or venetoclax and drug abuse and drug dependency are not available.

Preliminary efficacy data based on investigator assessment of radiographic data available as of 30 June 2013 are presented below for Study M12-175; efficacy data are not yet available for other venetoclax studies. In treatment Arm A, 54 of 56 patients were considered evaluable for response (i.e., completed the Week 6 evaluation or discontinued prior to Week 6). Objective response (OR) was reported in 46 of 54 evaluable patients (85.2%) in treatment Arm A: 5 patients (8.9%) experienced complete response (CR), 2 patients (3.7%) experienced CR with incomplete marrow recovery (CRi), and 39 patients (72.2%) experienced partial response (PR). In treatment Arm B, 32 patients with NHL were considered evaluable for response. OR was reported in 17 of 32 patients (53%) in treatment Arm B: 3 patients (9.4%) had a CR and 14 patients (53.7%) had a PR. All 8 patients (100%) with MCL in treatment Arm B experienced a PR.

Details and most current data are provided in the ABT-199/Venetoclax Investigator's Brochure.

1.2.2.4 Clinical Pharmacokinetics and Pharmacodynamics

Preliminary PK data for venetoclax are available from ongoing oncology Studies M12-175, M12-630, and M13-365 in patients with hematologic malignancies.

The venetoclax formulation currently used in clinical studies is a tablet formulation with strengths of 10, 50, and 100 mg. The tablet formulation was orally administered after a low-fat meal. Food increased the bioavailability of venetoclax by 3- to 4-fold. Preliminary PK results indicated that the absorption of venetoclax after the oral dosing was relatively slow. Venetoclax plasma concentrations peaked at approximately 6 hours after dosing. The mean terminal phase elimination half-life of venetoclax was approximately 17 hours and the mean oral clearance was approximately 13 L/hr after a single dose. There was no apparent difference in the pharmacokinetics of venetoclax between patients with CLL/SLL or NHL. The combined data from patients

with CLL/SLL and NHL suggested that venetoclax exposure was approximately dose proportional across the 150- to 900-mg dose levels. In the limited number of patients to date, co-administration of BR did not show apparent impact on venetoclax pharmacokinetics.

Details and most current data are provided in the ABT-199/Venetoclax Investigator's Brochure.

1.2.3 Obinutuzumab

1.2.3.1 Obinutuzumab Mechanism of Action

Obinutuzumab ([G], synonymous with GA101 and RO5072759; the term obinutuzumab will be used throughout the protocol) is a humanized and glycoengineered monoclonal antibody derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics ([Mössner et al. 2010](#)):

- High-affinity binding to CD20
- Type II binding to the CD20 epitope, leading to low complement-dependent cytotoxicity related to the recognition of the CD20 epitope and the lack of CD20 localization into lipid rafts after binding of the monoclonal antibody to CD20
- Compared with the chimeric Type I anti-CD20 antibody rituximab, increased antibody-dependent cell-mediated cytotoxicity (ADCC) related to an improved binding of obinutuzumab to the different allotypes of Fc γ RIIIa expressed by natural killer cells and monocytes
- Compared with rituximab, increased direct cell-death induction related to an elbow hinge amino exchange of the Fab region and Type II binding of the CD20 epitope

Given the significantly greater ADCC and direct cell-death induction, it is possible that obinutuzumab may have greater efficacy than rituximab, particularly in the 80%–85% of patients who are carriers of the Fc γ RIIIa low-affinity receptor polymorphism (FF/FV genotype), because such patients may have decreased overall survival (OS) compared with patients with the high-affinity (V/V) polymorphism who demonstrate improved survival following therapy with chemotherapy plus either rituximab or I¹³¹-tositumomab ([Persky et al. 2012](#)).

Obinutuzumab is currently being explored in lymphoid malignancies, such as DLBCL, FL, and CLL. Preliminary data suggest possible increased anti-lymphoma efficacy over rituximab, a hypothesis that is currently being explored in several randomized trials including a Phase III study of R-CHOP versus obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone (G-CHOP) in DLBCL (Study BO21005).

1.2.3.2 Obinutuzumab Nonclinical Toxicology

The nonclinical toxicology of obinutuzumab has been evaluated in repeat-dose studies in cynomolgus monkeys given weekly intravenously (30-minute infusion) for up to 26 weeks in duration and weekly SC injections for 4 weeks in duration. The high dose of

50 mg/kg in the 26-week study resulted in a steady-state AUC from Time 0 to 24 hours (AUC₀₋₂₄) exposure of 341,000 µg • hr/mL that is approximately 61-fold above that of the clinical exposure of 5584 µg • hr/mL.

Consistent with expected pharmacological activity, obinutuzumab caused marked decreases in B cells with corresponding lymphoid depletion in spleen and lymph nodes. Circulating CD40-positive mature B cells began to reverse after several months without treatment and maximally reversed to 7%–152% of baseline by 37 weeks. In addition, transient decreases in natural killer (NK) cells were observed; this finding is consistent with the pharmacological effect of FcγRIIIa binding. Suspected opportunistic infections in as many as three unscheduled deaths were considered a possible secondary result of B-cell depletion.

Obinutuzumab was immunogenic in the cynomolgus monkey; this immunogenicity led to reduced systemic exposures in several animals and abrogation of the pharmacological activity. Hypersensitivity reactions were noted that included systemic inflammation and infiltrates consistent with immune-complex-mediated hypersensitivity reactions such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation and led to unscheduled termination in 6 animals.

Both the clinical IV formulation of obinutuzumab and the SC formulation were locally well tolerated across studies. No effects were present in male and female reproductive parameters included in the 26-week IV-dose study. No obinutuzumab-related effects were observed on CNS, respiratory, or cardiovascular (CV) functions.

Significant increases in cytokine secretion caused by obinutuzumab were measured in *in vitro* assays with the use of undiluted human whole blood, indicating that obinutuzumab has an increased propensity to trigger first infusion-related cytokine release in patients.

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

1.2.3.3 Obinutuzumab Nonclinical Efficacy

Obinutuzumab has demonstrated *in vivo* efficacy superior to rituximab in various human lymphoma xenograft models. Both antibodies were tested in human SUDHL-4 cells (a DLBCL model) subcutaneously injected in severe combined immunodeficient beige mice. Rituximab administration was started when tumors were established and rapidly growing. Results showed that rituximab at 10 mg/kg inhibited tumor growth compared with rituximab at 1 mg/kg; however, increasing the rituximab dose to 30 mg/kg did not result in increased efficacy. In contrast, obinutuzumab showed a dose-dependent increase in efficacy in the range of 1–30 mg/kg. Results showed complete tumor regression in all animals and lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

Additional studies have also shown similar results, with obinutuzumab treatment controlling tumor growth, whereas vehicle- and rituximab-treated tumors were not controlled ([Mössner et al. 2010](#)).

See the Obinutuzumab Investigator's Brochure for details on the nonclinical studies.

1.2.3.4 Obinutuzumab Clinical Experience

As of July 2013, more than 1900 patients with CD20-positive malignant disease have been treated with obinutuzumab in clinical trials. Clinical data for obinutuzumab are available from six clinical trials including three Phase I and/or Phase II studies of obinutuzumab monotherapy, a Phase Ib chemotherapy combination study in NHL (Study BO21000), and two Phase III studies (Study BO21004 in CLL and Study GA04753g in NHL).

Infusion-related reactions (IRRs), mostly Grades 1 and 2, are the most common adverse events observed during therapy. IRRs have been associated predominantly with the first infusion and generally occur early during the infusion, shortly after the infusion, or, in some cases, up to 24 hours after the completion of the infusion. In a few patients, concurrent signs of laboratory TLS were observed. The incidence and intensity of IRRs decreased with subsequent infusions of obinutuzumab. Other frequently observed adverse events include infections and neutropenia. On the basis of preliminary observations, extensive tumor burden may be a predisposing factor for the occurrence of some IRRs. Grades 3–4 thrombocytopenia and neutropenia, including febrile neutropenia, have been reported with obinutuzumab and were associated predominantly with treatment of CLL rather than NHL. Given its anticipated mode of action that results in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections during and after treatment.

Data from Study BO20999 (obinutuzumab monotherapy) showed safety and efficacy of single-agent obinutuzumab in patients with relapsed indolent and aggressive lymphomas. Responses were seen at both lower (400 mg) and higher (800 and 1600 mg) doses, although responses increased at the higher dose, with 54% of patients with indolent lymphoma and 32% of patients with aggressive lymphomas showing PR or CR at end of treatment ([Morschhauser et al. 2013](#); [Salles et al. 2013](#)).

Study BO21000 evaluated obinutuzumab in combination with chemotherapy, both fludarabine/cyclophosphamide and CHOP ([Radford et al. 2013](#)). Both chemotherapy combinations were shown to be feasible in patients with previously untreated or relapsed/refractory FL with response rates of >90% for both regimens. Safety was acceptable with no new or unexpected adverse effects observed. The most common adverse event was neutropenia.

Data from obinutuzumab in combination with chlorambucil in patients with CLL (Study BO21004) showed increased efficacy of the combination over chlorambucil alone

with a hazard ratio for PFS of 0.14. IRRs were common and neutropenia occurred at increased frequency with the combination therapy, but there was no increase in infections or treatment-related deaths.

See the Obinutuzumab Investigator's Brochure for additional details on the clinical studies.

1.2.3.5 Obinutuzumab Pharmacokinetics and Pharmacodynamics

A two-compartment model comprising a time-varying clearance pathway and a linear clearance pathway provides an adequate description of the pharmacokinetics of obinutuzumab following IV administration in Studies BO20999 and BO21003. Following the infusion of obinutuzumab, the elimination appears to be characterized by a linear clearance pathway that is dependent on time (i.e., starting at a typical value of 630 mL/day and then gradually decreasing to an asymptote of 60 mL/day at steady state). Tumor burden may potentially contribute significantly to the clearance of obinutuzumab, especially at the beginning of treatment when CD20-positive tumor cells are most abundant. As tumor burden decreases, the clearance reaches an asymptote that is believed to be primarily a function of the proteolytic metabolic clearance. Therefore, some patients with a high tumor burden may appear to clear the drug from the plasma faster than patients with a low tumor burden because obinutuzumab binds to the CD20-positive tumor cells and is effectively removed from the plasma. Therefore, the clearance of the drug will vary with time, because repeated treatments with obinutuzumab will reduce the quantity of CD20-positive tumor cells. Consequently, the number of obinutuzumab administrations during the first cycle of treatment may be expected to reduce the number of CD20-positive tumor cells, thus minimizing the impact of the time-varying clearance pathway on obinutuzumab exposure.

Treatment with obinutuzumab resulted in extensive B-cell depletion, with all patients showing a reduction in B-cell counts to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before and after infusion, but transient changes have been observed in the levels of interleukin (IL)-6 and IL-8 before and after infusion.

1.3 STUDY RATIONALE

B-cell NHL cells, including DLBCL, express CD20 antigen. Anti-CD20 therapy (rituximab) has been demonstrated to provide enhanced anti-tumor activity in combination with other agents targeting the disease (Coiffier et al. 2002; Hiddemann et al. 2005), leading to acceptance of R-CHOP as standard of care in most DLBCL and a common choice of therapy for other B-cell NHL. However, significant room for improvement exists. *BCL2* is overexpressed in most FL and many DLBCLs as a consequence of the t(14;18) chromosomal translocation or gene amplification and is associated with a poor prognosis in DLBCL (Iqbal et al. 2011). Bcl-2 is likely to play a role in resistance to the pro-apoptotic activities of chemoimmunotherapeutic regimens, such as R-CHOP. Therefore, the addition of a Bcl-2 inhibitor to R-CHOP has the potential to significantly

enhance the anti-leukemic activity of the regimen and to result in improved clinical outcomes. Navitoclax is an inhibitor of Bcl-2 previously studied in the clinic that, because of its concomitant inhibition of Bcl-xL (a survival factor for platelets), causes dose-related thrombocytopenia. Nonclinical data supporting the combination of R-CHOP and Bcl-2 inhibitors include murine xenograft models that demonstrated significantly improved anti-lymphoma activity of the combination of R-CHOP and navitoclax (ABT-263) over the activity of either treatment regimen alone ([Ackler et al. 2010](#)).

Obinutuzumab is currently being compared with rituximab in combination with CHOP chemotherapy in a randomized trial in patients with DLBCL (Study BO21005). If obinutuzumab proves to be superior to rituximab, the standard of care would change to G-CHOP. Therefore, the combination of venetoclax with both R-CHOP and G-CHOP will be examined in this study.

DLBCL is a molecularly heterogeneous disease, with a variety of molecular subtypes identified through gene expression profiling ([Rosenwald et al. 2002](#)). The two major subtypes, GCB and ABC, show activation of oncogenic and survival pathways that differ from each other and are associated with different prognoses. Although evidence for a prognostic effect of Bcl-2 is greatest in the GCB subtype, both GCB and ABC DLBCL overexpress Bcl-2 in approximately 50% of cases, arguing for biological relevance of Bcl-2 in both subtypes. The implications of Bcl-2 inhibition in each subtype are unknown; therefore, after the appropriate dose is identified, the combination will be investigated in an expanded cohort with enough patients in each molecular subgroup to obtain preliminary information regarding activity in each group.

This study will explore the safety of the combination of venetoclax plus R-CHOP or G-CHOP in patients with B-cell NHL who are believed to be appropriate candidates for R-CHOP therapy during initial dose-finding cohorts and will further explore safety and efficacy in Phase II cohorts of patients with previously untreated DLBCL in order to identify appropriate populations for evaluation in a Phase III setting. In addition, efficacy of venetoclax plus R-CHOP in the subgroup of patients with *DE*-DLBCL will be explored. *DE*-DLBCL is a recently defined poor prognostic subgroup, characterized in part by overexpression of Bcl-2, for whom the addition of venetoclax might add substantial therapeutic benefit.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of the Phase I portion of the study is the following:

- To estimate the maximum tolerated dosing schedule for venetoclax given in combination with R-CHOP or G-CHOP to patients with B-cell NHL, either previously untreated or relapsed/refractory after a maximum of one prior therapy

The primary objectives of the Phase II portion of the study are the following:

- To assess the safety and tolerability of the combination of venetoclax and R-CHOP or G-CHOP administered to patients with previously untreated DLBCL
- To make a preliminary assessment of efficacy as measured by CR rate *at end of treatment* determined by positron emission tomography and/or computed tomography (PET-CT) scans (see [Appendix 2](#)) of the combination of venetoclax and R-CHOP administered to patients with previously untreated DLBCL
- To make an assessment of efficacy, as measured by CR rates *at end of treatment* determined by PET-CT scans, of the combination of venetoclax and R-CHOP administered to patients with previously untreated DLBCL co-expressing both Bcl-2 and c-Myc proteins (i.e., *DE*-DLBCL)

2.2 SECONDARY OBJECTIVES

2.2.1 Pharmacokinetic Objectives

The PK objectives of this study are the following:

- To characterize the pharmacokinetics of venetoclax and relevant metabolites when administered in combination with R-CHOP or G-CHOP in the relapsed/refractory or previously untreated setting in NHL
- To characterize the pharmacokinetics of rituximab, obinutuzumab, and prednisone when administered in combination with venetoclax in patients with relapsed/refractory or previously untreated B-cell NHL
- To confirm exposure to cyclophosphamide, doxorubicin, and vincristine when given in combination with rituximab, obinutuzumab, and/or venetoclax

2.2.2 Secondary Efficacy Objectives

The secondary efficacy objectives of this study include the following:

- To make a preliminary assessment of efficacy when venetoclax and R-CHOP are administered in combination to patients with previously untreated DLBCL, as measured by:
 - OR rate
 - CR rate as determined by CT scan
 - DOR*
 - PFS
 - 12 month PFS estimate*
 - OS
- To make a preliminary assessment of efficacy when venetoclax and G-CHOP are administered in combination, as measured by OR rate, CR rate, and PFS.

2.2.3 Exploratory Objectives

The exploratory objectives of this study are the following:

- To make a preliminary assessment of potential biomarkers that might predict disease response or resistance to treatment with the venetoclax plus R-CHOP or G-CHOP combinations in the relapsed or previously untreated setting:
 - Bcl-2 and Bcl-2 family protein expression, including Bcl-xl and Mcl-1, by immunohistochemistry (IHC)
 - BCL2* and c-MYC copy number gain by fluorescence in situ hybridization (FISH) and translocation t(14;18) by FISH
 - Expression of transcripts for Bcl-2 family members, other apoptotic genes, and genes associated with ABC or GCB subtypes of DLBCL
 - Subgroups relevant to DLBCL biology that are defined genetically or by poor prognosis, including CD79b, Myd88, CARD11, TNFAIP3, epigenetic markers, and MYC translocation
- To make a preliminary assessment of the efficacy of venetoclax and R-CHOP in different potential prognostic subgroups, including DLBCL genotypic subtypes (e.g., ABC; GCB), high Bcl-2 (Bcl-2-positive) expression, as well as patients displaying *BCL2* and MYC translocations (Double Hit)
- To make a preliminary assessment of minimal residual disease (MRD) as a prognostic marker in DLBCL
- To evaluate the prognostic significance of interim PET assessment in this setting

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib/II, multicenter, open-label, dose-finding study of venetoclax administered orally in combination with rituximab or obinutuzumab and standard doses of CHOP in patients with NHL. The study will consist of two stages: a dose-finding Phase Ib stage and a Phase II expansion stage. In the Phase I portion of the study, two parallel treatment arms will explore doses of venetoclax ranging from 200 to 800 mg administered in combination with R-CHOP and G-CHOP (see [Figure 1](#)). Patients will be treated for a total of eight cycles (six cycles of CHOP and eight cycles of venetoclax+ rituximab or venetoclax+ obinutuzumab). Each cycle will consist of 21 days. Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor. The maximum tolerated dose (MTD) of venetoclax in combination with R-CHOP and G-CHOP will be determined separately for each arm during the dose-finding stage.

The dose and dose schedule for venetoclax for each arm determined in Phase I will be used in the Phase II expansion stage for that arm.

For the Phase II portion of the study, the venetoclax dose for Arm A is 800 mg on a non-continuous dosing schedule of Cycle 1 Days 4–10 and Cycles 2–8 Days 1–10, as determined by the Phase Ib portion of the study based on safety and tolerability observed in patients treated in the dose escalation portion of the study (see Section 3.2.3 for justification).

If there are concerns about the tolerability of the Phase II dose at any time during the Phase II study, a lower dose or an alternative dosing schedule for venetoclax + R-CHOP or G-CHOP may be explored on a case by case basis based on the guideline provided in Section 4.3.

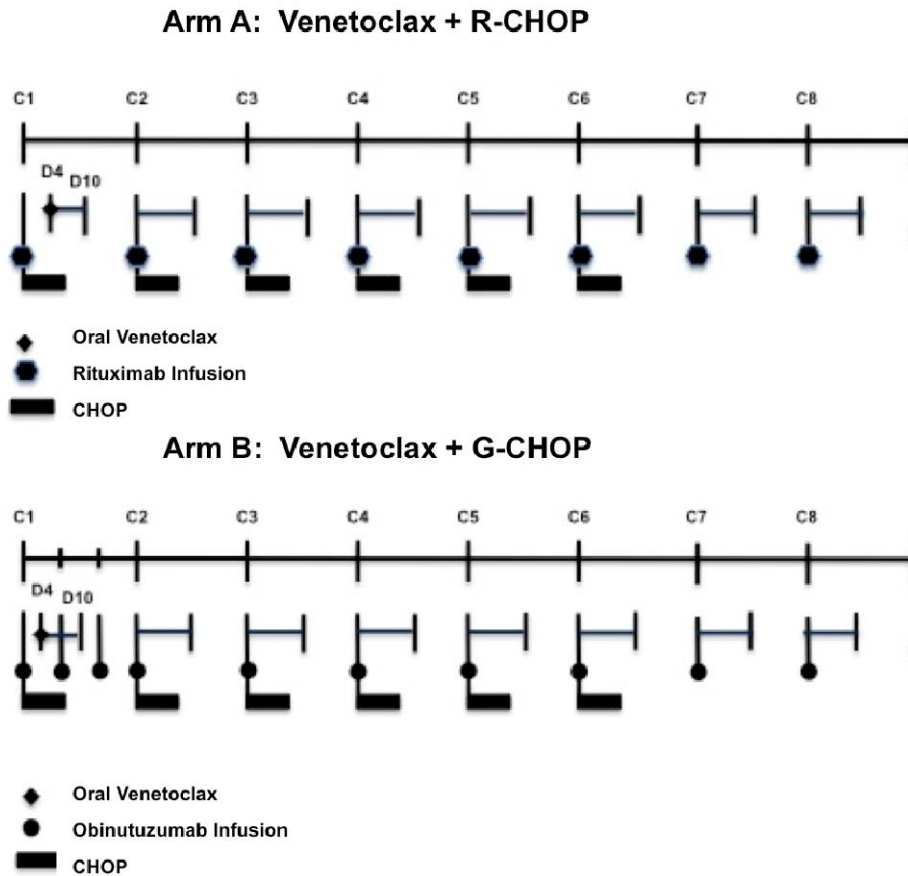
For the Phase II R-CHOP arm of the study, after the first 20 patients have completed Cycles 1 and 2 of study treatment, the Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC; see Section 3.1.1) will meet to review safety data for all patients treated in both the Phase Ib and Phase II portions of the study in order to confirm the safety and tolerability of the combination therapy at the venetoclax dose chosen at the end of Phase Ib. Enrollment will continue while the interim safety analysis is being conducted.

On the basis of this review, changes may be made to the dose or the dosing schedule of the Phase II (see Section 3.2.3).

3.1.1 Internal Monitoring Committee and Scientific Oversight Committee

An IMC and a SOC will be established to monitor patient safety in both phases of the study. The IMC and SOC will provide a recommendation for each treatment arm on the venetoclax dose to be taken forward into the Phase II portion of the study after completion of the dose-escalation phase and will provide a further recommendation at the Phase II interim safety analysis on the safety of this dose. The IMC will include the Sponsor's Medical Monitor and at least one other medical doctor/Clinical Science representative not directly involved in the study as well as representatives from drug safety, biostatistics, and statistical programming and analysis. The IMC will continue to conduct periodic interim reviews of safety data quarterly during Phase II or more frequently as needed. The SOC will comprise experts in DLBCL who are investigators for this study in order to provide guidance and a review of safety-related events. Separate SOC/IMC agreements will outline each committee's composition, meeting timelines, and members' roles and responsibilities. The committee members will review all potential cases of serious adverse events, Grade 3 and 4 adverse events, and deaths as specified in the SOC/IMC agreement. The SOC will be kept apprised of all relevant efficacy and safety data from this study and other related clinical trials. Ad hoc meetings may be called in addition to scheduled meetings as necessary to provide recommendations on management of any new safety issues. The Sponsor will make final decisions regarding protocol procedures and modifications.

Figure 1 Study Schema



C=cycle; D=day; G=obinutuzumab; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; R=rituximab.

The study will consist of two stages: a dose-finding Phase Ib stage and a Phase II expansion stage. The MTD of venetoclax in combination with R-CHOP and G-CHOP will be determined separately for each arm during the dose-finding stage. The MTD and dosing schedule for venetoclax for each arm will be used in the Phase II stage for that arm, unless safety or tolerability signals suggest a lower dose will be more appropriate when combining with R-CHOP and G-CHOP. The study will enroll approximately 24–60 patients during the dose-finding stage and approximately 180–200 patients in the Phase II portion at approximately 69 investigative sites in North America, the European Union, and Asia Pacific.

Patients will be evaluated for safety, tolerability, and pharmacokinetics of study treatment. Assessments for anti-tumor activity will be performed following four cycles of study treatment (i.e., during Cycle 4, between Days 15 and 21) and at the completion of study treatment.

3.1.2 Phase Ib: Dose-Finding

Each study arm (R-CHOP in Arm A or G-CHOP in Arm B) will have four dose-finding cohorts exploring venetoclax doses *and dosing schedules* ranging from 200 to 800 mg-*with a maximum dose administration schedule of 10 days per cycle*. Patients will be allocated to a study arm in sequential fashion, starting with Arm A, Cohort 1. Priority for enrollment when more than one arm is open to enrollment will be Arm A followed by Arm B. In previous studies conducted with single-agent venetoclax, TLS has been observed after the first dose, particularly in patients with CLL at doses ≥ 50 mg/day. Clinically significant TLS was not observed in patients with NHL, other than in MCL; therefore, patients with MCL are excluded from this study. However, TLS is a known risk following initiation of chemotherapy and anti-CD20 therapy in DLBCL. It is possible that, with the combination of venetoclax and chemoimmunotherapy, an increased rate and severity of TLS could occur. In order to mitigate the risk for TLS, venetoclax will be initiated following initiation of CHOP (see Section 3.1.2.1). Additional prophylactic measures for mitigating the risk of TLS are described in Section 4.4.1.2.

3.1.2.1 Cohort Dosing Regimen Cycle 1

- Patients in the R-CHOP arm will receive the first rituximab infusion (375 mg/m²), administered per package insert (along with standard premedications) on Day 1 (Cycle 1 Day 1). Rituximab administration guidelines are outlined in Section 4.3.2.2.
- Patients in the G-CHOP arm will receive their first obinutuzumab infusion (1000 mg) on Day 1 (Cycle 1 Day 1) along with standard premedication. During Cycle 1, obinutuzumab will also be administered on Days 8 and 15. Obinutuzumab administration guidelines are outlined in Section 4.3.3.
- Note: On the basis of a risk assessment for TLS and IRR by the investigator, patients with high tumor burden or those who cannot tolerate the full dose of rituximab or obinutuzumab in a single day because of adverse events may receive the antibody infusion split over 2 days or receive the first cycle as an inpatient, if necessary.
- Following rituximab or obinutuzumab infusion, patients will receive CHOP chemotherapy, per standard administration procedures, along with standard premedications (see Section 4.3.4). Note that the first prednisone dose for each cycle should be administered prior to rituximab or obinutuzumab.
- Oral dosing of venetoclax will start on Day 4 of the first cycle (Cycle 1 Day 4). In the event that CHOP dosing is delayed (for any reason), initiation of venetoclax dosing should also be delayed and then started 3 days following CHOP. For example, if CHOP is first administered on Day 2, venetoclax dosing should be started on Day 5. Patients will be monitored for signs of acute TLS for at least 8 hours after the first venetoclax dose (see Section 4.4.1.2).
- Oral dosing of venetoclax will then continue through Day 10 of Cycle 1 and Days 1-10 of Cycles 2 through 8 *or alternative dose administration schedules, that*

include oral administration of venetoclax on Days 4–8 in Cycle 1 and Days 1–5 in Cycles 2–8.

- Guidelines for TLS prophylaxis were modified for high-risk TLS patients to consider starting at a lower dose of venetoclax and reaching the specified dose in a step-wise fashion in discussion with the Medical Monitor to prevent or promptly treat TLS (see Section 4.4.1.5)

Cycles 2–6

Patients will continue to receive an oral dose of venetoclax on Days 1-10. On Day 1 of each cycle, venetoclax will be administered prior to any infusions. Rituximab or obinutuzumab will be administered on Day 1 along with CHOP per standard administration guidelines.

Cycles 7–8

Patients will continue to receive an oral dose of venetoclax on Days 1-10. On Day 1 of Cycles 7 and 8, venetoclax will be administered prior to infusion of rituximab or obinutuzumab. Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor.

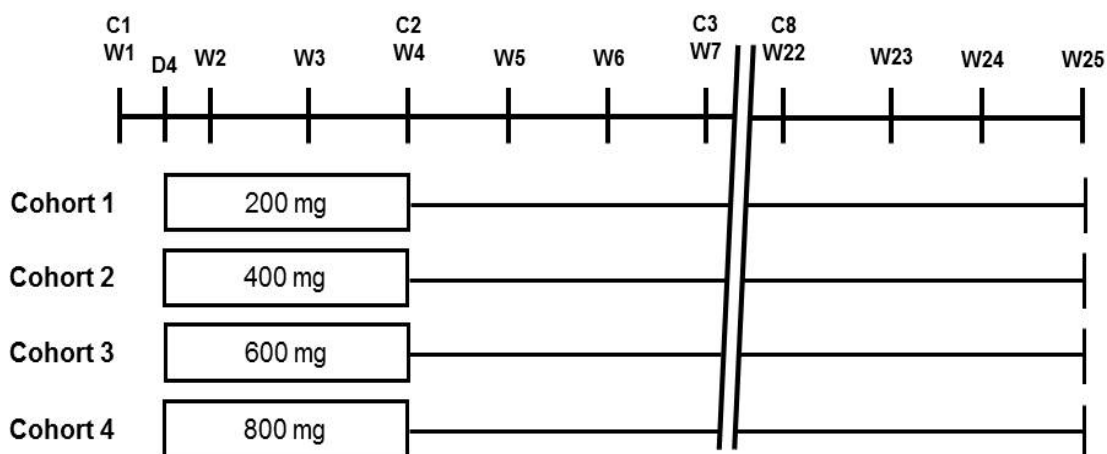
On days that pre-dose PK sampling is required, venetoclax and prednisone dosing will occur in the clinic to facilitate PK sampling.

Patients should be pre-medicated with antihistamines and acetaminophen (corticosteroids if necessary) for rituximab infusion per the package insert, per Section 4.3.3.6 for obinutuzumab infusion, and with anti-emetics and IV hydration per institutional policy and standard of practice.

3.1.2.2 Dose-Escalation Guidelines

Dosing with venetoclax will begin on Day 4 of Cycle 1 (or 3 days after the first CHOP dose, see Section 3.1.2.1) and continue to be administered daily through Day 8 or Day 10 of Cycle 1 and then on Days 1–5 or Days 1–10 for Cycles 2–8 for up to eight 21-day cycles of combination therapy with R-CHOP or G-CHOP. For each arm, if the cohort dosing regimen is determined to be tolerable and to not exceed the MTD (as described in Section 3.1.2.3), dose escalation of venetoclax will proceed to the subsequent cohorts. All subsequent cohorts will start venetoclax on Day 4 of Cycle 1 (or 3 days after the first CHOP dose; see Section 3.1.2.1 and Figure 2). Venetoclax will continue to be administered at the target cohort dose schedule through Cycle 8 (Cycle 8 Day 10).

Figure 2 Venetoclax Dose-Finding Cohorts



C=cycle; D=day; W=week.

If the administration of venetoclax results in unacceptable toxicity on Days 4–10 of Cycle 1 and Days 1–10 of Cycles 2-8 schedule *or other proposed alternative dose administration schedules* then alternative dose regimens of venetoclax (e.g., venetoclax administered on Days 1–3 or 1–7 of 21) or lower doses of venetoclax may be substituted in subsequent cohorts. If clinically significant TLS is observed at initiation of the administration of venetoclax, alternative doses and dose administration schedules will be explored (e.g., initiate the administration of a lower dose with a gradual dose escalation to the target dose). If clinically significant TLS is not observed in this study in the initial cohorts then venetoclax dosing starting at Cycle 1 Day 1 or Day 2 may be explored. If venetoclax dosing starts at Cycle 1 Day 1 or 2 then the DLT observation period would be shortened to one cycle) (see Section 3.4.1.1). Dose modification of R-CHOP or G-CHOP (delays and reductions) because of myelosuppression will be made per Section 4.5.6.

3.1.2.3 Dose-Escalation Rules and Determination of Dose-Limiting Toxicity

The following dose-escalation rules will apply:

- DLTs in this study are defined as qualifying events occurring during the DLT observation period (see Section 3.1.2.4) experienced during combination therapy with venetoclax plus R-CHOP or G-CHOP.
- Dose escalation will be pursued using a modified 3+3 design. At least 3 patients will be enrolled in each arm per Cohort. Additional patients may be enrolled at each dose level/dose schedule.
- If none of the first 3 evaluable patients experience a DLT during the DLT observation period prior to dose escalation (0 of at least 3 patients), then the next dose cohort (as described in Section 3.1.2.1) may be evaluated. Available data from all patients receiving study drug will be considered in dose escalation decisions.

- If DLT is observed in 1 patient at a given dose level during the DLT observation period prior to dose escalation, additional patients will be enrolled at that dose level until at least 6 evaluable patients have completed the DLT observation window or until a second DLT occurs.
- If no additional patients experience a DLT during the DLT observation period (≤ 1 of at least 6 evaluable patients), then the next dose cohort (as described in Section 3.1.2.1) may be evaluated.
- If an additional DLT is observed after expanding beyond 3 evaluable patients (≥ 2 DLTs out of at least 6 evaluable patients or in one-third or more of patients if the cohort includes more than 6 patients), further enrollment at that dose schedule will be halted and that dose will either be declared as exceeding the MTD or a different dose administration regimen will be implemented, in which case dose escalation may resume.

Alternative dose administration regimens (e.g., shorter non-continuous dose administration of venetoclax) may be explored, as described in Section 3.1.2.2, depending upon the toxicity profile observed.

Dose cohorts resulting in DLTs in less than one-third of a minimum of 6 patients will be considered for further study in the Phase II part of the study.

The highest (or most dose-intensive) dose administration regimen that results in DLTs in less than one-third of a minimum of 6 patients will be declared the MTD.

3.1.2.4 Definition of Dose-Limiting Toxicity

All adverse events, including DLTs, are to be reported according to instructions in Section 5.1.3 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). If a patient experiences a DLT, he or she will be treated according to clinical practice and will be monitored for resolution of the toxicity. Decrease in B cells, lymphopenia, and leukopenia caused by lymphopenia will not be considered DLTs but instead are expected pharmacodynamic outcomes of study treatment. Any Grade ≥ 3 adverse event that is attributed to having a reasonable possibility of being related to the combined administration of venetoclax plus R-CHOP or G-CHOP, that cannot be attributed by the investigator to an alternative, clearly identifiable cause such as tumor progression, concurrent illness or medical condition, or concomitant medication and that occurs during the DLT observation period (beginning of venetoclax administration through the end of Cycle 2) will be considered a DLT for dose-escalation purposes. Grade 3 or 4 neutropenia or thrombocytopenia identified on Day 1 of Cycle 2 or 3, resulting in dose delay is considered a DLT.

The following events are exceptions and will not be considered DLTs:

- Grade 3 or 4 lymphopenia, which is an expected outcome of therapy
- Grade 3 or 4 neutropenia that is not accompanied by temperature elevation (oral or tympanic temperature of $\geq 100.4^{\circ}\text{F}$ [38°C]) and improves to Grade ≤ 2 (or to $\geq 80\%$ of the baseline value, whichever is lower) by Day 1 of the next cycle
- Grade 3 neutropenic fever
- Grade 3 or 4 leukopenia as a result of lymphocyte depletion
- Grade 3 or 4 thrombocytopenia that does not result in bleeding and improves to Grade ≤ 2 (or to $\geq 80\%$ of the baseline value, whichever is lower) by Day 1 of the next cycle without platelet transfusion
- Grade 3 or 4 anemia
- Grade 3 laboratory TLS without manifestations of clinical TLS (i.e., creatinine ≥ 1.5 times the upper limit of normal [ULN] and/or renal dysfunction, cardiac arrhythmias, seizures, or sudden death)
- Grade 3 nausea or vomiting ≤ 7 days (in the absence of premedication or that can be managed with oral or IV anti-emetics)
- Reversible Grade 3 infusion related toxicities (including symptoms such as fever, chills/rigors, nausea, vomiting, pruritus, headache, rhinitis, rash, and hypotension) occurring during or within 24 hours after completing an infusion and resolving within 24 hours with a reduced infusion rate, supportive care, and/or administration of corticosteroids

If a patient experiences a DLT as described above, the patient will be observed for resolution of the toxicity. If the DLT resolves to Grade ≤ 2 (or $\geq 80\%$ of the baseline value) within 2 weeks and it is determined to be in the patient's best interest to continue study treatment (after discussion between the treating investigator and the Medical Monitor), the patient may continue to receive study treatment, provided that the study treatment dose modifications are made as agreed to between the investigator(s) and the Medical Monitor.

If Grade 3 or 4 neutropenia and/or thrombocytopenia that do not meet the definition of a DLT are observed in a patient receiving combination treatment, the patient may continue to receive treatment, provided the neutropenia and/or thrombocytopenia has resolved to Grade ≤ 2 (or $\geq 80\%$ of the baseline value, whichever is lower) within the time frame described above. Guidelines for dose reduction of R-CHOP or G-CHOP are provided in Section [4.3.3.3](#).

3.1.3 Phase II: Expansion

The Phase II portion of the study will consist of one cohort for each study arm (R-CHOP and G-CHOP) with the use of the established venetoclax dosing schedule identified during the dose-finding stage for that arm in patients with previously untreated DLBCL. If both arms are open to Phase II enrollment, patients will be assigned to Arm A

(venetoclax+R-CHOP) or Arm B (venetoclax+G-CHOP) through randomization. If only one arm is open to Phase II enrollment at a given time, then patients will be directly assigned to the open arm. The Phase II portion will enroll only patients with previously untreated DLBCL. Because effects of Bcl-2 inhibition may differ depending on both the level of Bcl-2 expression and the molecular milieu (see Section 1.3), activity of the combination will be explored in specific molecular subsets, including Bcl-2 high, Bcl-2 low, Bcl-2- *overexpression* and c-Myc overexpression (DE), and GCB and ABC subtypes of DLBCL.

Enrollment into the R-CHOP cohort of patients with both Bcl-2 high and Bcl-2 low DLBCL will continue until approximately 50 patients with DE-DLBCL (approximately 160–200 patients total; see Section 4.10.6. Bcl-2 and c-Myc expression analysis results will not be required prior to enrolling patients in the Phase II cohorts. It is estimated that approximately 50% of patients with DLBCL will have high expression of Bcl-2, and that approximately 20%–30% of patients with DLBCL will have high expression of both Bcl-2 and c-Myc (DE).

Patients will be monitored for safety and tolerability during the study, including ability to maintain relative dose intensity of the chemotherapy (CHOP) backbone. After 20 patients on Arm A of the Phase II portion of the study have completed the first two cycles of study treatment, an interim safety analysis of all patients treated to date on both the Phase Ib and Phase II portions of the study will be conducted in order to confirm the safety and tolerability of the venetoclax Phase II dose in the combination. Enrollment will continue while the interim safety analysis is being conducted.

If there are concerns about the tolerability of the Phase II dose at any time during the Phase II study, a lower dose or an alternative dosing schedule for venetoclax+R-CHOP or G-CHOP may be explored on a case by case basis based on the guideline provided in Section 4.3.

Disease assessments will be performed 15–21 days after completion of Cycle 4 dosing (interim response assessment) and 6–8 weeks after Day 1 of the last cycle received (end-of-treatment response). Thereafter, patients will be followed in the clinic every 3 months for safety and disease assessments for up to 2 years after the last patient *has completed* treatment or until death or study termination, whichever occurs first.

3.1.4 Discontinuation of Venetoclax plus R-CHOP or G-CHOP

Patients who discontinue venetoclax plus R-CHOP or venetoclax plus G-CHOP for reasons other than PD should *have a documented response assessment and continue to be followed* until disease progression *even after* institution of alternative therapy. These *patients* should continue with follow-up visits every 3 months to collect information on disease progression *and /or* initiation of an alternative lymphoma therapy. *After PD, patients will also continue to be followed for OS* (see Section 4.5.5).

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Benefit/Risk Assessment

This study combines treatments that have demonstrated clinical activity against B-cell NHL in general and DLBCL in particular: R-CHOP chemoimmunotherapy is one of the standard treatment regimens for B-cell NHL, and the experimental agent venetoclax is a specific inhibitor of the Bcl-2 anti-apoptotic protein expressed in many NHL cells. Bcl-2 overexpression is likely to play a role in resistance to the pro-apoptotic activities of chemoimmunotherapeutic regimens such as R-CHOP. In parallel, the substitution of obinutuzumab—a novel anti-CD20 monoclonal antibody that has shown significant promise in B-cell malignancies—for rituximab will be tested in this regimen. Obinutuzumab is currently being compared with rituximab in combination with CHOP in a Phase III study in patients with previously untreated DLBCL and if results of this study demonstrate superiority of obinutuzumab, the G-CHOP regimen will be used in future studies of the combination. The addition of a Bcl-2 inhibitor to R-CHOP or G-CHOP has the potential to significantly enhance the anti-lymphoma activity of the regimen and to result in improved clinical outcomes.

Nonclinical data support the rationale for improved efficacy and for tolerability, respectively, of the combination of R-CHOP and the Bcl-2/Bcl-xL dual inhibitor navitoclax (see Section 1.3). Because venetoclax is a specific inhibitor of Bcl-2 and does not appreciably inhibit Bcl-xL, it is predicted that dose-limiting thrombocytopenia may be avoided or reduced relative to navitoclax, allowing for a potentially greater therapeutic index and increased clinical efficacy compared with either R-CHOP alone or the combination with navitoclax.

Principal risks identified for the combination regimen of R-CHOP or G-CHOP with venetoclax include: TLS, infusion reactions to rituximab or obinutuzumab, cytopenias, (i.e., neutropenia, thrombocytopenia, or lymphopenia), infections, other malignancies, and drug interactions with CYP3A4 inhibitors or inducers (venetoclax). In addition, there is a theoretical concern for potentiation of anthracycline-induced cardiotoxicity. The protocol includes the following features to address these risks:

- Measures to prevent TLS include use of prophylactic hydration and medication prior to initial dosing with careful monitoring during the first 24 hours after dosing for metabolic or clinical signs of impending TLS (see Section 4.4.1.5). In addition, dosing of venetoclax will be staggered; venetoclax dosing will be initiated 3 days after the first CHOP dose (see Section 3.1.2.1) during the first cycle of chemoimmunotherapy in all cohorts for both R-CHOP and G-CHOP arms. If clinically significant TLS is not observed in this study in the initial cohorts then venetoclax dosing starting at Cycle 1 Day 1 or Day 2 may be explored. Guidelines for TLS prophylaxis were modified for high-risk TLS patients to consider starting at a lower dose of venetoclax and reaching the specified dose in a step-wise fashion in discussion with the Medical Monitor to prevent or promptly treat TLS (see Section 4.4.1.5)

- Prophylactic medication (see Section 4.3.3) will be administered and careful monitoring guidelines will be used to manage infusion reactions for rituximab or obinutuzumab.
- Frequent blood testing throughout the treatment period will monitor for cytopenias. Dose delays or dose reductions are mandated for severe cytopenias. In addition, all supportive measures including transfusion, antibiotics, and the use of growth factors are allowed. Guidelines for venetoclax dose modification due to thrombocytopenia are listed in Section 4.3.6 (see Table 3).
- Anti-infection prophylaxis is not mandated for all patients because of the potential risks of adding additional concomitant medications but may be prescribed by the investigator in specific cases where patients are at especially high risk. Patients with preexisting infections are excluded from the study to avoid reactivation. Neutropenia will be closely monitored and may be treated with growth factors, and any signs of infection will be treated with appropriate medication.
- Guidelines for concomitant medications to avoid or use with caution are provided in view of the possible drug-drug interactions (see Appendix 5).

The venetoclax + R-CHOP or G-CHOP treatment combinations are expected to be associated with toxicities that can largely be managed (e.g., first-dose TLS and infusion reactions) or that are commonly encountered with the treatment of NHL and that can be mitigated with the measures outlined in this protocol. In particular, infection and cytopenias are common during the treatment of NHL with chemoimmunotherapy as a result of myelosuppressive effects of the treatment. The potential advantage of this regimen is that the addition of a Bcl-2 inhibitor may facilitate targeted cell killing of high-Bcl-2 expressing NHL cells without the need to further increase myelosuppression over what is observed with R-CHOP.

As discussed in Section 1.1.2, although DLBCL is curable in many patients, those who are not cured have extremely poor outcomes, arguing for urgent incorporation of novel therapies. Because the likelihood of curing DLBCL is known to be impacted by maintenance of dose intensity of standard chemotherapy, dose intensity will be monitored on a regular basis by the IMC/SOC (see Section 4.10.4.2), and evidence of excessive dose delays or reductions would prompt modification of the trial.

Because many patients with B-cell NHL are not cured with standard therapy, the benefit of a novel therapy with the potential to evade chemotherapy resistance through the incorporation of the Bcl-2 inhibitor outweighs the risks expected from this combination regimen and supports initiation of this Phase Ib/II study.

3.2.2 Rationale for Venetoclax Dose Selection in the Phase I Portion of the Study

Venetoclax dosing for this study was determined on the basis of the experience from the Phase I study (Study M12-175) with single-agent venetoclax in relapsed/refractory patients with NHL. This study explored a step-up dosing schedule in order to safely

administer venetoclax by reducing the risk for TLS showing safety of initial doses of up to 400 mg without clinically significant TLS in NHL. Final target doses of up to 800 mg have been shown to be tolerable in patients with CLL. Patients with NHL have received final target doses of 1200 mg without DLTs. The starting dose will be 200 mg. Subsequent dose cohorts will explore progressively higher starting and target doses up to a final dose of 800 mg, if tolerated. Given that venetoclax will be administered in conjunction with R-CHOP or G-CHOP chemoimmunotherapy, which on its own has a degree of myelosuppression, venetoclax dosed up to the MTD achieved as monotherapy may not be tolerable in this combination. The number of cycles of dosing (eight 3-week cycles) is designed to provide treatment duration consistent with other therapies for NHL that have been shown to be sufficient to provide durable responses.

3.2.3 Rationale for Venetoclax Dose Selection in the Phase II Portion of the Study

As per study design description (see Section 3.1), the MTD and dosing schedule for venetoclax for each arm will be used in the Phase II stage for that arm, unless safety or tolerability signals suggest a lower dose would be more appropriate when combined with R-CHOP and G-CHOP.

In the Phase Ib dose-escalation portion of the study, none of the dose levels studied exceeded the MTD on the non-continuous dosing schedule. Since no MTD could be identified at any dose-level tested, and since it was considered unlikely that higher doses of venetoclax would provide an improved benefit/risk profile, on the basis of the data from the other clinical studies of venetoclax in NHL, the 800-mg dose was selected for the R-CHOP arm.

Overall, the combination of R-CHOP with venetoclax administered on the non-continuous schedule was well tolerated. However, two adverse events were noted to occur at increased frequency than would be expected with R-CHOP alone and were likely because of the combination therapy: diarrhea and thrombocytopenia. These toxicities were adequately managed with medical intervention and dose interruptions, but following review by the IMC/SOC, further dose escalation was not felt to be indicated. Guidelines for management of these events are provided in Table 3 and Section 4.4.1.8.

Therefore, on the basis of safety and tolerability observed in patients treated in the dose-escalation portion of the study, the Phase II venetoclax dose for Arm A (venetoclax+R-CHOP) is 800 mg on a non-continuous dosing schedule of Cycle 1 Days 4–10 and Cycles 2–8 Days 1–10. In M12-175 (single agent venetoclax) study responses were observed in DLBCL with single agent venetoclax doses that range from 600 mg to 1200 mg with no evidence of improved responses at doses higher than 600 mg.

In order to confirm that the Phase II dose is safe and tolerable, a safety interim analysis will be performed after 20 patients enrolled in Phase II Arm A have completed two cycles

of combination therapy. During this analysis, data will be reviewed for all patients in both arms enrolled in the study in order to assess safety and tolerability of the combination in a larger number of patients. In addition, review of data from patients treated on the Phase Ib portion of the study will allow assessment of longer-term tolerability of the combination throughout the planned treatment course, including incidence of dose delays or dose reductions in later cycles. Enrollment will continue while the interim safety analysis is being conducted.

An IMC and SOC (see Section 3.1.1) will meet to review safety data for all patients treated in both the Phase Ib and Phase II portions of the study in order to confirm the safety and tolerability of the combination therapy at the Phase II dose. Given the results from this analysis, the Sponsor may decide to decrease the dose or the dosing schedule of the Phase II part of the study.

In addition, the SOC and the IMC will conduct periodic interim reviews of safety data during Phase II (see Section 3.1.1). Given the results from these reviews, the Sponsor may decide to decrease the dose or dosing schedule of the Phase II part of the study.

On 17 July 2016, Roche/Genentech as the sponsor of Study BO21005 (Goya study), a Phase III study that evaluated G-CHOP versus R-CHOP in 1L DLBCL, informed through a press release that the primary endpoint of investigator-assessed PFS was not met. Given these results, Arm B (venetoclax +G-CHOP) will not be expanded in Phase II in patients who are first-line with-DLBCL.

3.2.4 Rationale for R-CHOP Dosing

R-CHOP will be administered at standard dose on a standard 21-day cycle schedule. CHOP chemotherapy will be given for six cycles, with eight total cycles of rituximab (Pfreundschuh et al. 2008). Six cycles of CHOP chemotherapy have been chosen for this study on the basis of National Comprehensive Cancer Network guidelines for the United States. However, because global standards of care differ when a 21-day schedule for R-CHOP is used and because no comparative data regarding number of cycles are available using R-CHOP–21, patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor.

3.2.5 Rationale for G-CHOP Dosing

G-CHOP is being studied in two ongoing clinical studies in patients with DLBCL. In both studies, CHOP is administered at standard doses and schedule. The dose and schedule for obinutuzumab in this regimen is 1000 mg on Days 1, 8, and 15 of Cycle 1 and Day 1 of each cycle thereafter for a total of eight cycles of obinutuzumab. This dose and schedule were chosen for the following reasons:

- In Study BO20999, patients were randomized to two different obinutuzumab dose cohorts. In the low-dose (LD) cohort, patients received eight cycles of 400 mg of

obinutuzumab, with an additional 400-mg dose given on Day 8 of the first cycle. In the HD cohort, obinutuzumab was given at 1600 mg on Days 1 and 8 of the first cycle, followed by 800 mg at Cycles 2–8. No DLTs were observed between the two doses and, although there was a slight increase of IRRs and neutropenia rates in the HD cohort, obinutuzumab was generally very well tolerated. As expected, PK variability was lower at the higher dose. Importantly, an increased overall response rate was observed in the HD cohort compared with the LD cohort (55% vs. 13%, respectively) in the subset of patients with indolent lymphoma and a trend toward better response rates in the HD cohort was observed in patients with aggressive lymphomas, arguing that a higher dose is more effective and not significantly more toxic.

- In the HD cohort of Study BO20999, the first two doses of obinutuzumab were set at 1600 mg. Although well tolerated by patients, the dose administration scheme resulted in dose administration times of ≥ 5 hours. With the goal of maintaining the loading dose concept and to provide a significant amount of antibody early in the treatment course, it was decided to split the obinutuzumab dose administration and to change the schedule and dose during the first 2 weeks of any future studies from 1600 mg administered on Days 1 and 8 to 1000 mg administered on Days 1, 8, and 15. This dosing regimen may provide comparably fast rising PK exposure and early target saturation, while avoiding the practical challenges of delivering 1600 mg of drug in a single day together with chemotherapy. The dose administered for subsequent cycles is also set at 1000 mg. This dose and schedule will result in an obinutuzumab exposure of 3000 mg during the first 2 weeks for a cumulative exposure of 10,000 mg and is therefore very close to the regimen that has delivered the best results thus far for obinutuzumab in both indolent and aggressive lymphoma. There is no indication that the additional obinutuzumab doses administered on Days 8 and 15 in the first cycle would negatively affect the safety of patients.

Results reported to date in these ongoing studies suggest that this dose administration schedule is tolerable. In order to maintain consistency with these studies, the same dosing schedule will be administered in the current study.

3.2.6 Rationale for Dosing Schedule

Both venetoclax plus R-CHOP/G-CHOP demonstrate rapid response of malignant and normal peripheral B lymphocytes after initial administration. TLS has been observed following initiation of both R-CHOP and venetoclax in both FL and DLBCL, but the frequency and severity of TLS related to venetoclax is expected to be less than that seen with CLL. Staggered dosing of venetoclax will be administered, as described in Section 3.1.2.2. If clinically significant TLS is not observed in this study in the initial cohorts then venetoclax dosing starting at Cycle 1 Day 1 or Day 2 may be explored. Patients will receive TLS prophylaxis with hydration and a uric acid-lowering agent at least 72 hours prior to the first dose of venetoclax. The venetoclax dose administration schedule was changed to administering venetoclax in Cycle 1 on Days 4–10 and

Cycles 2–8 on Days 1–10 due to as a result of toxicities observed in the first cohort of 200 mg of venetoclax under continual daily dosing.

3.2.7 Rationale for Treatment of Patients with Previously Untreated DLBCL

DLBCL is potentially curable, with approximately 60% of patients having long-term remissions following standard treatment with R-CHOP. Patients with intermediate to high risk by the IPI have a lower chance of cure with R-CHOP therapy than those with low IPI, and patients who relapse or are refractory to R-CHOP have very poor outcomes, with most dying within 2 years ([Gisselbrecht et al. 2010](#)). Better treatments are urgently needed for these patients. Bcl-2 is overexpressed in most DLBCL and likely plays a role in resistance. Therefore, exploring this combination in first-line DLBCL is compelling. Given the potential for cure of these patients with standard therapy and the importance of maintaining dose and schedule of R-CHOP, a critical issue in exploring the combination with venetoclax is to minimize the chance for dose delays or reductions. It is critical to explore the tolerability of this combination in the proposed Phase II cohorts in order to demonstrate the feasibility of dose maintenance before embarking on a large Phase III study in the future.

3.2.8 Rationale for Pharmacokinetic Assessments

The risk of clinically significant PK drug interaction between venetoclax, rituximab, or obinutuzumab and CHOP is expected to be low on the basis of their metabolic pathways. Venetoclax is primarily metabolized by CYP3A4 and is a reversible inhibitor of CYP2C8 and CYP2C9. Rituximab and obinutuzumab are biologics administered intravenously and are not expected to modulate CYP3A4 activity and affect venetoclax metabolism. Prednisone has been implicated as potential weak CYP3A4 inducer and/or an inducer of P-gp, which could result in reduced venetoclax concentrations depending on the prednisone dose and timing relative to venetoclax administration and the duration of the induction effect after prednisone dosing is stopped.

Rituximab and obinutuzumab have decreased clearance with time that may be related to CD20 target expression and tumor burden. Venetoclax may affect the clearance of rituximab and obinutuzumab because it has the potential to decrease tumor burden. PK samples for rituximab and obinutuzumab will be collected to assess whether drug levels differ from the combination compared with historical data to check for potential drug-drug interactions.

Drug-drug interaction potential between venetoclax and prednisone will also be explored in this study. PK samples for prednisone will be collected on Cycle 1 Day 1 (before administration of venetoclax) and Cycle 2 Day 1 (when administered with venetoclax).

PK samples to assess the plasma/serum levels of venetoclax, rituximab, obinutuzumab, and CHOP components will be collected according to the schedule in [Appendix 3](#).

Alternative PK assessments may be explored if there is substantial difficulty in obtaining the time points listed in [Appendix 3](#).

3.2.9 Rationale for Collecting Tumor Biopsies and Peripheral Blood for Biomarker Studies

DE-DLBCL, defined as Bcl-2 high and c-Myc high protein, are associated with poor outcomes in DLBCL. Identifying these DE patients is a primary objective of this study. It is estimated that approximately 50% of patients with DLBCL will have high expression of Bcl-2, and that approximately 20%–30% of patients with DLBCL will have high expression of both Bcl-2 and c-Myc (DE). Bcl-2 is also associated with poor prognosis ([Iqbal et al. 2011](#)). The t(14;18) translocation, which places the *BCL2* gene under the control of the immunoglobulin heavy chain enhancer, is found in the GCB subtype of DLBCL; amplification of the 18q21 locus where the *BCL2* gene resides are found in the ABC subtype. Together, somatic genetic aberrations are found in 30%–40% of patients with DLBCL, and whereas, both result in overexpression of Bcl-2 at the mRNA and protein levels, Bcl-2 expression is associated with a poorer prognosis in the GCB subtype. Therefore, the efficacy of therapy in high Bcl-2 (Bcl-2 positive) and in different prognostic subgroups, including ABC/GCB, will be important to help identify the target population for Phase III that will most likely benefit from venetoclax in combination with R-CHOP or G-CHOP.

Venetoclax inhibits the ability of cancer cells to evade cell death, or apoptosis, by blocking the activity of the anti-apoptotic protein Bcl-2. Nonclinical studies have demonstrated a pattern of response to venetoclax on the basis of genetic aberrations in Bcl-2, Bcl-2 protein levels, and the levels of Bcl-2 family proteins ([Souers et al. 2013](#)). High levels of Bcl-2 and low levels of Mcl-1 are generally predictive of response to Bcl-2 inhibitors in vitro ([Mérino et al. 2012](#)), and loss of expression of proteins involved in mitochondrial apoptosis and/or upregulation of Mcl-1 is associated with resistance. In addition, high levels of at least one pro-apoptotic “sensor,” such as Noxa or Bim, is required. The following relevant DNA, RNA, and proteins (including Bcl-2 and prognostic subgroups) will be measured at baseline to identify biomarkers that predict efficacy and, when available, also at relapse to understand mechanisms of resistance:

- Bcl-2 and c-Myc protein expression by IHC
- Bcl-2 and Bcl-2 family protein expression by IHC
- *BCL2* and *c-MYC* copy number gain by FISH and translocation t(14;18) by FISH
- Expression of transcripts for *BCL2* family members, other apoptotic genes, and genes associated with the ABC or GCB subtypes of DLBCL
- Subgroups relevant to DLBCL biology that are defined genetically or by poor prognosis including CD79b, Myd88, CARD11, TNFAIP3, epigenetic markers, and MYC translocation

MRD may have prognostic value in DLBCL. In patients with an identifiable IgH rearrangement, clonal IgH rearrangements may be used as a marker of MRD. In

the Phase II portion of this study, peripheral blood samples will be collected for MRD at baseline, Cycle 4 Day 1, 6–8 weeks following Cycle 8 Day 1, and every 3 months during follow-up for 1 year.

The following samples will be collected to enable the evaluation of the parameters listed above:

- A tumor biopsy sample (either archival or fresh) must be collected from all patients. The tumor specimen must contain adequate evaluable tumor cells to enable Bcl-2 IHC and other relevant biomarker analysis. Samples can be in a tissue block (preferred) or prepared as 20 unstained serial slides, and should be accompanied by an associated pathology report. The specimen must be a formalin-fixed, paraffin-embedded tumor specimen, or another appropriate fixative must be used (notation of the type of fixative should be included). Cytological or fine-needle aspiration as well as bone marrow samples are not acceptable.
- In the Phase II portion of this study, a tissue punch sample must be collected from the tissue block in patients who have an excisional biopsy sample available.
- The tissue punch must be submitted to the pathology central laboratory for construction of tissue microarrays (TMAs). Instructions for tissue punch will be provided in the laboratory manual.
- *An FFPE tumor biopsy sample must be collected at disease progression and sent to the central laboratory to evaluate venetoclax resistance mechanisms. The sample must be a tissue block or 20 unstained serial slides.*
- Blood collection to evaluate blood-based approaches to classification of ABC/GCB and other DLBCL subgroups
- Plasma collection at Baseline, Cycle 5, and at relapse to evaluate circulating tumor markers that could be associated with response/resistance including but not limited to mutations in *BCL2*

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety and tolerability of the combination of venetoclax plus R-CHOP or G-CHOP will be assessed using the following primary safety outcome measure:

- Incidence and nature of combination DLTs

In addition, safety will be assessed using the following secondary safety outcome measures:

- Incidence, nature, and severity of adverse events and serious adverse events graded according to NCI CTCAE v4.0. Adverse events of special interest include Grade 4 neutropenic fever, Grade ≥ 3 IRRs to rituximab or obinutuzumab, and Grade ≥ 4 TLS.
- Change in clinical laboratory results (including hematology and chemistry) and vital signs

- Maintenance of relative dose intensity of CHOP chemotherapy

3.3.2 Pharmacokinetic Outcome Measures

The following PK parameters will be derived from the plasma concentration-time profile of prednisone, venetoclax, and relevant metabolites following administration when appropriate, as data allow:

- Total plasma exposure (AUC)
- Time to maximum observed plasma concentration (t_{max})
- C_{max} in plasma
- Minimum plasma concentration under steady-state conditions within a dosing interval (C_{min}) in plasma

The following PK parameters will be determined from the concentration-time profiles of rituximab, obinutuzumab, and CHO components, as applicable:

- C_{max} in serum or plasma, as appropriate
- C_{min} in serum or plasma, as appropriate

Other PK parameters such as clearance, volume of distribution (V), and half-life may also be calculated as data allow.

3.3.3 Efficacy Outcome Measures

The following activity outcome measures will be assessed:

- Primary outcome measures:
 - CR, as defined by PET-CT scan as well as bone marrow examination when applicable (see [Appendix 2](#))
- Secondary outcome measures:
 - CR, as defined by CT scan and bone marrow examination, when applicable
 - OR, defined as a PR or CR
 - DOR, defined as the first occurrence of a documented response until the time of relapse or death from any cause
 - PFS, defined as the time from date of first dose of study drug to the first occurrence of progression, relapse, or death while in the study, where death while in the study is defined as death from any cause within 12 weeks of the last tumor assessment
 - PFS at 12 months
 - Relative dose intensity
 - OS, defined as the time from date of first dose of study drug until the date of death from any cause. For patients who have not died, survival data will be censored at the date of last contact.

OR and disease progression will be determined with use of the modified Lugano Classification: Revised Criteria for Response Assessment ([Cheson et al. 2014](#); see [Appendix 2](#)).

3.3.4 Exploratory Assessments

The following correlative biology measures will be assessed:

- Bcl-2 high (Bcl-2 positive) as defined by IHC and Bcl-2 family protein expression by IHC
- *BCL2* and c-MYC copy number gain by FISH and translocation t(14;18) by FISH
- Expression of transcripts for Bcl-2 family members, other apoptotic genes, and genes associated with the ABC or GCB subtypes of DLBCL
- Subgroups relevant to DLBCL biology, including CD79b, Myd88, CARD11, TNFAIP3, epigenetic markers, and MYC translocation

3.4 SAFETY PLAN

Patients who are enrolled in this study will be carefully monitored during the entire study, and any new information from this and other studies will be communicated to sites and will result in protocol modifications as necessary to ensure appropriate risk-mitigation procedures. Safety evaluations will consist of medical interviews, collection of adverse event information, physical examinations, vital sign assessments, and laboratory tests, including hematologic, biochemical, and immunologic assessments. Patients will be evaluated for adverse events at each study visit through 30 days after the last dose of venetoclax study treatment or the last dose of CHOP or 90 days after the last rituximab or obinutuzumab study treatment, whichever is later.

During the dose-finding stage, F. Hoffmann-La Roche Ltd (Sponsor) will hold teleconferences with investigators for evaluation of each dose level to review toxicities. Additional ad hoc teleconferences will be held as necessary to discuss any ongoing issues regarding toxicity or study conduct. In addition, an IMC and SOC will be established to review all safety data and make recommendations regarding dose selection of venetoclax. Access to safety data will be available to the Medical Monitor via the electronic data capture (EDC) system. All serious adverse events will be reviewed by the Medical Monitor within 24–48 hours after reporting, and serious, unexpected, related adverse events will be reviewed for regulatory reporting purposes. Regular teleconferences will be held with investigators, study sites, and the Medical Monitor to review toxicities observed in patients in the study and to discuss decisions regarding dose and schedule modifications.

During the Phase II portion of the study, all patients will continue to be monitored for safety and tolerability. Precautionary safety measures and regular monitoring of safety by an IMC and the Sponsor enable early identification of safety signals in the study and minimize the risk to patient enrolled. An IMC/SOC Agreement will be developed to establish the detailed roles and responsibilities of the IMC and the SOC.

See Section 5 for complete details of the safety evaluation for this study.

3.4.1 Risks Associated with Venetoclax and Their Management

The clinical safety profile of venetoclax based on clinical data obtained in the ongoing Phase I studies is summarized in Section 1.2.2.3. On the basis of clinical data to date, the known and suspected risks are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 4.3.6. See the ABT-199/GDC-0199 Investigator's Brochure for complete and updated details.

3.4.1.1 Tumor Lysis Syndrome

The principal DLT associated with venetoclax in the ongoing Phase I Study M12-175 to date has been TLS (in patients with CLL/SLL), primarily, but not exclusively related to the first dose.

Experience from the Phase I study has suggested that clinically significant TLS is less common in NHL than in CLL; however, laboratory TLS has been observed in some patients with NHL. The combination of venetoclax with effective chemotherapy and a monoclonal antibody, which may also cause TLS in patients with NHL, raises the possibility of more significant occurrences of TLS. All patients must receive hydration and an agent to reduce uric acid as TLS prophylaxis at least 72 hours prior to starting venetoclax treatment. Laboratory testing is required after initial dosing to monitor for metabolic changes and will be used to assess the need for closer monitoring and hospitalization for IV hydration and treatment of metabolic abnormalities caused by rapid cell lysis. Hospitalization will be required at initial venetoclax dosing for patients who are determined to be at high risk of TLS as a result of bulky disease (i.e., any lymphoma mass ≥ 10 cm *and/or* evidence of circulating lymphoma cells). See Section 4.4.1.5 for details of the TLS prophylaxis and monitoring schedule to be used for initial dosing.

3.4.1.2 Cytopenias

Lymphopenia, neutropenia, thrombocytopenia, and anemia have been reported in the Phase I study conducted in heavily pretreated patients with CLL and NHL. In certain cases, the condition was preexisting. In this study, blood counts will be monitored closely throughout treatment. Growth factors are permitted according to local practice, and patients will be monitored and treated promptly in case of infections (see Section 4.4.1.3). Blood counts that meet DLT requirements will result in dose changes. It is recommended that blood counts be checked within 24-72 hours for patients with cytopenias that result in dose delays to see if the counts have recovered.

3.4.1.3 Infections

Infections of various types have occurred in patients in the Phase I study. NHL can be associated with impaired immune function and increased infections, and it is unclear whether or how much the incidence could be increased as a result of venetoclax treatment. Patients in this study will be closely monitored for infections, and

prompt therapy will be instituted, as necessary. Patients are allowed to receive concomitant prophylactic anti-infective therapy at the investigator's discretion (see Section [4.4.1.6](#)).

3.4.1.4 Decreased Spermatogenesis

There is a potential for decreased spermatogenesis without recovery with the use of venetoclax. Male patients considering preservation of fertility should bank sperm before treatment.

3.4.1.5 Drug-Drug Interaction

Co-administration of venetoclax with strong and moderate CYP3A inhibitors (see [Appendix 5](#) for examples) is not recommended. Consider alternative medications. If the patient requires use of these medications, use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration.

If the patient requires use of strong or moderate CYP3A inducers (see [Appendix 5](#) for examples), use with caution and contact the Medical Monitor for guidance.

3.4.2 Risks Associated with Rituximab Therapy and Their Management

3.4.2.1 Infusion-Related Reactions

In single-agent clinical studies of rituximab and in post-marketing surveillance studies, mild to moderate IRRs consisting of fever and chills/rigors occurred in the majority of patients during the first rituximab infusion. Other frequent IRR signs and symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30–120 minutes of beginning the first infusion, and they resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, meperidine, and vasopressors). The incidence of IRRs was highest during the first infusion and decreased with each subsequent infusion.

Rituximab has caused severe IRRs. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes. Signs and symptoms of severe IRRs may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm and may require interruption of rituximab administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events (see [Appendix 4](#)). Approximately 80% of fatal IRRs occurred in association with the first infusion of rituximab.

3.4.2.1.1 Management of Severe Infusion-Related Reactions

Administration of rituximab will occur in a setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies. The rituximab infusion should be interrupted for severe reactions. Medications and supportive care measures including but not limited to epinephrine, antihistamines, glucocorticoids, IV fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available for immediate use and instituted as medically indicated for use in the event of a reaction during administration. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients who require close monitoring during the first and all subsequent infusions include patients with preexisting cardiac and pulmonary conditions, patients with prior clinically significant cardiopulmonary adverse events, and patients with high numbers of circulating malignant cells ($\geq 25,000$ cells/ μL) with or without evidence of high tumor burden.

3.4.2.2 Tumor Lysis Syndrome

Rapid reductions in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia have been reported within 12-24 hours after the first infusion of rituximab. Rare instances of a fatal outcome have been reported in the setting of TLS following treatment with rituximab. The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells ($\geq 25,000$ cells/ μL) or high tumor burden. Prophylaxis for TLS including hydration and administration of a uric acid-lowering agent is required in this study for all patients. A lower starting dose of venetoclax may be used in high-risk TLS patients (see Section 4.4.1.5). Patients deemed to be at high risk for TLS complications may, at the investigator's discretion, receive their initial dose of rituximab over 2 consecutive days (see Section 4.3.2.3). Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of the complications of TLS, rituximab has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

3.4.2.3 Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported for some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy (Yeo et al. 2009).

All patients will be screened for HBV infection by measuring hepatitis B surface antigen (HBsAg), total anti-hepatitis B core antibodies (anti-HBc), and total anti-hepatitis B surface antibodies before initiating treatment with rituximab or obinutuzumab. For patients who show evidence of prior hepatitis B infection (i.e., with positive total hepatitis B core antibody [HBcAb], negative HBsAg and undetectable HBV DNA), a consult is

required with a physician who has expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy. These patients will be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following rituximab therapy (see Section 4.4.1.7). HBV reactivation has been reported up to 24 months following completion of therapy. In patients who develop reactivation of HBV while on rituximab, immediately discontinue rituximab and any concomitant chemotherapy and institute appropriate treatment (see Table 3). Insufficient data exist regarding the safety of resuming rituximab or obinutuzumab in patients who develop HBV reactivation.

Additional serious viral infections, either new, reactivated, or exacerbated (e.g., infections caused by cytomegalovirus, varicella zoster virus, herpes simplex virus, West Nile virus, parvovirus B19, John Cunningham [JC] virus, and hepatitis C virus) have been reported with rituximab, mainly in patients who had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The risk of such infections with rituximab in combination with chemotherapy and venetoclax is unknown. Particular attention should be given to patients who have had significant prior immunosuppressive treatment such as HD chemotherapy and stem cell transplant. JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has been observed in rituximab-treated patients with hematologic malignancies or with autoimmune diseases. Most cases of PML were diagnosed within 12 months following the patient's last infusion of rituximab. Physicians should consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes but is not limited to consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Physicians should discontinue rituximab or obinutuzumab (and chemotherapy and venetoclax) and consider discontinuation or reduction of any immunosuppressive therapy in patients who develop PML.

3.4.2.4 Cardiovascular Events

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

3.4.2.5 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, were observed in patients who received rituximab in combination with chemotherapy for DLBCL. In post-marketing reports, which include patients with low-grade or follicular NHL and patients with DLBCL, the mean time to onset of symptoms was 6 days (range, 1–77 days) in patients with documented gastrointestinal perforation. Complaints

of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

3.4.2.6 Immunization

The safety of immunization with live viral vaccines following rituximab therapy has not been studied. Patients who participate in this study may not receive either primary or booster vaccination with live virus vaccines for at least 6 months prior to initiation of rituximab or at any time during study treatment. Investigators should review the vaccination status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases prior to study therapy.

Refer to the Rituxan[®]/MabThera[®] Package Insert/Summary of Package Characteristics for additional safety information.

3.4.3 Risks Associated with Obinutuzumab Therapy

There may be additional potential health risks, including hitherto unknown risks, derived from exposure to obinutuzumab.

3.4.3.1 Infusion-Related Reactions and Hypersensitivity Reactions (Including Anaphylaxis)

The commonly experienced IRRs associated with obinutuzumab are characterized by hypotension, fever, chills, flushing, nausea, vomiting, hypertension, and fatigue, among other symptoms. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g., anaphylaxis). IRRs generally appear early during the infusion or shortly after, or in some cases, up to 24 hours after the completion of obinutuzumab infusion. Some patients have developed severe IRRs resulting in permanent discontinuation of obinutuzumab. In some instances, concurrent signs of TLS are observed.

In the majority of patients, IRRs were mild or moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs that required symptomatic treatment have also been reported.

Respiratory infusion-related symptoms such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema have also been reported. These IRRs were mostly mild or moderate (NCI CTCAE v4.0, Grade 1 and 2 events), and < 10% of the events were severe (Grade 3 events), occurring predominantly during the first hour of the infusion or shortly after the first infusion had finished; the events resolved with slowing or interruption of the infusion and supportive care. The incidence and severity of IRRs decreased with subsequent infusions. Extensive tumor burden predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in patients with CLL) may be a predisposing factor for the development of IRRs.

Hypersensitivity may be difficult to distinguish from IRRs; however, anaphylaxis has been reported in patients treated with obinutuzumab. If a hypersensitivity reaction is suspected during infusion (e.g., symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped and treatment permanently discontinued. Patients with known IgE-mediated hypersensitivity to obinutuzumab should not be treated.

3.4.3.2 Tumor Lysis Syndrome

Cases of TLS have been reported with obinutuzumab administration. To date, no patient has required hemodialysis for renal failure. Patients with a high tumor burden, including patients with a lymphocyte count of $\geq 25 \times 10^9/L$ (particularly, patients with B-cell CLL and MCL), are at increased risk for TLS and severe IRRs.

3.4.3.3 Thrombocytopenia and Neutropenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia, (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in patients treated with obinutuzumab. The greatest risk of hemorrhage in obinutuzumab-treated patients seems to be during the first cycle, although a clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients treated with concomitant medication that could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle. If an event of thrombocytopenia occurs, 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.

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has been observed predominantly in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2 or baseline. Use of granulocyte-colony stimulating factor (G-CSF) has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab (see Section 4.4.1.3).

3.4.3.4 Anti-Therapeutic Antibody

Although obinutuzumab is a fully humanized antibody, there is a risk that anti-therapeutic antibodies could develop, thus reducing efficacy and/or resulting in symptomatic hypersensitivity reactions. Experience with similar humanized antibodies (e.g., trastuzumab) suggests that the incidence and titer of such antibodies will be low and will be unlikely to affect efficacy or cause unwanted immunological reactions (Genentech data on file).

3.4.3.5 Infection

On the basis of its anticipated mode of action that results in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients who received obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections (e.g., cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B or C) have been reported with the B cell–depleting antibody rituximab, mainly in patients who had received the drug in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The risk of such infections with obinutuzumab is unknown. Physicians should be aware of symptoms suggestive of PML and consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes but is not limited to consultation with a neurologist, brain MRI, and lumbar puncture.

3.4.3.6 Gastrointestinal Perforation

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

3.4.4 Risks Associated with CHOP Chemotherapy

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

Common side effects of CHOP include fever, infection, hair loss, nausea and/or vomiting, constipation, and potential neurologic, lung, liver, and cardiac toxicity. Patients treated with doxorubicin, an anthracycline-based chemotherapy, are at risk for cardiotoxicity. Although the risk increases with cumulative dose, irreversible cardiotoxicity may occur at any dose level. Patients with preexisting heart disease, hypertension, concurrent administration of other anti-neoplastic agents, prior or concurrent chest irradiation, and advanced age are at increased risk.

3.4.5 Risks Associated with the Combination of Venetoclax plus R-CHOP or G-CHOP

This Phase Ib/II study will assess the toxicities associated with the combination of venetoclax plus R-CHOP or G-CHOP. Given their mechanisms of action and single-agent safety profiles, additive or overlapping acute toxicities for the combination of venetoclax plus R-CHOP or G-CHOP could potentially include neutropenia and TLS. The risk of TLS will be mitigated by starting treatment with one agent before the other, to allow some reduction of disease burden before the second agent is added. In addition, patients will receive hydration and TLS prophylaxis prior to initial dosing (see Section 4.4.1.5).

In terms of chronic toxicity, it is theoretically possible that inhibition of Bcl-2 could enhance and/or prolong neutropenia and lymphopenia following completion of R-CHOP or G-CHOP treatment. These effects, if they occur, could likely manifest as an increased incidence of infections. All patients will be monitored closely for infection and treated aggressively according to institutional guidelines. WBC growth factor support will be used for all patients.

If clinically indicated, anti-infective prophylaxis should be implemented at the investigator's discretion, including appropriate prophylaxis for viral, fungal, bacterial, or pneumocystis infections. The Medical Monitor should be notified if these infections are observed. Potential for drug-drug interactions should be considered (e.g., azoles for fungal prophylaxis). See [Appendix 5](#) for a list of excluded and cautionary medications.

In addition, there has been some indication of mild decrease in cardiac contractility following treatment with venetoclax in animal models, though not at this time in humans. Myocardial toxicity is a recognized dose-related toxicity of anthracyclines such as doxorubicin. The combination could theoretically, therefore, potentiate cardiotoxicity. Since no cardiotoxicity was noted in the Phase I part of the study, only a baseline cardiac evaluation with multiple-gated acquisition (MUGA) scan or echocardiogram will be performed, unless additional studies are clinically indicated during treatment.

Potential for drug-drug interactions should be considered (e.g., azoles for fungal prophylaxis). Drug interactions may occur with CYP3A4 inhibitors or inducers (venetoclax). The risk of clinically significant PK drug interaction between venetoclax, rituximab, obinutuzumab, and CHOP is expected to be low on the basis of their metabolic pathways. Rituximab has decreased clearance with time that may be related to CD20 target expression and tumor burden. Venetoclax may affect the clearance of rituximab because it has the potential to decrease tumor burden. Similar considerations may be relevant for obinutuzumab clearance. Because the agents in this study have not been administered before in combination in patients with NHL, PK samples will be collected to assess whether drug levels differ from the combination compared with historical data to check for potential drug-drug interactions. See [Appendix 5](#) for a list of excluded and cautionary medications.

See Section [5](#) for complete details of the safety evaluation for this study.

3.5 ETHICAL CONSIDERATIONS

Any information obtained from this research will be treated as confidential. The information collected will not be provided to any third parties, such as insurers or employers (other than those required by law), but will be provided to health authorities (e.g., the European Medicine Authority or U.S. Food and Drug Administration [FDA]), Roche, AbbVie, and their collaborators.

This clinical research involves the procurement of samples of blood and lymph node samples for evaluation of Bcl-2 and other relevant biomarkers that help to understand how the patient's DLBCL behaves or responds to treatment. DNA samples will not be identified with patients' names, pictures, or any government-issued identification numbers (e.g., Social Security Number). Samples will be identified using the patient's year of birth and a unique sample identification number only (these are considered patient identifiers under the U.S. Health Insurance Portability and Accountability Act [HIPAA]). Samples will be linked with clinical data from the Sponsor's clinical study database (including outcome data) by the patient's year of birth and study identification number.

3.6 ADMINISTRATIVE STRUCTURE

In the U.S., this trial will be sponsored and managed by Genentech. F. Hoffmann-La Roche Ltd will sponsor this trial outside of the U.S. with management responsibilities being shared by Genentech and Roche. Genentech and Roche have authorized Roche Registrations, a company formed under the laws of England, to act as their legally authorized representative for the purposes of Article 19 of Directive 2001/20/EC relating to the implementation of Good Clinical Practice (GCP) in the conduct of clinical trials on medicinal products for human use. Reference to "Sponsor" in this protocol will mean Genentech for the United States and F. Hoffmann-La Roche Ltd for all countries outside of the United States.

Approximately 69 sites in North America, the European Union, and Asia Pacific will participate in this study to enroll approximately 290 patients. Data will be recorded via an EDC system from Medidata Solutions (New York, NY) with use of electronic Case Report Forms (eCRFs; see Section 6.6). Central laboratories will be used for the analyses of and/or management of PK, pharmacodynamic, genotyping, and tissue samples. An interactive voice/Web response system (IxRS) will be used for patient registration, patient number, and dose assignment.

3.7 INDEPENDENT REVIEW COMMITTEE

An IRC composed of board-certified radiologists and oncologists with experience in malignant lymphoma will assess all patients for response and progression on the basis of imaging results, bone marrow biopsy results, and relevant clinical data and will be guided by a charter specific to the independent review.

3.8 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the International Conference on Harmonisation (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. 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).

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Patient Selection

Patients who are in conformance with the following eligibility requirements may enroll in this study.

4.1.2 Inclusion Criteria

4.1.2.1 Patients Enrolled in the Dose-Finding Portion of the Study

Patients must have histologically confirmed B-cell NHL (and have never received R-CHOP treatment), except MCL or SLL, in order to enroll in this portion of the study.

Any relapsed/refractory patients who are enrolled during the dose escalation should have received only a single previous treatment regimen.

4.1.2.2 Patients Enrolled in the Phase II Portion of the Study

Patients must have previously untreated CD20-positive DLBCL and IPI score must be 2–5 in order to enroll in this portion of the study.

4.1.2.3 All Patients

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form(s)
- At least one bi-dimensionally measurable *lymphoma* lesion on CT scan defined as > 1.5 cm in its longest dimension, *which is also FDG avid by screening PET scan.*
- Ability and willingness to comply with the study protocol procedures
- Age ≥ 18 years
- Confirmed availability of archival or freshly biopsied tumor tissue meeting protocol-defined-specifications prior to study enrollment (see Section 4.1.4)
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
- Adequate hematologic function (unless caused by underlying disease, as established by extensive bone marrow involvement or as a result of hypersplenism secondary to the involvement of the spleen by lymphoma per the investigator) defined as follows:

Hemoglobin ≥ 9 g/dL

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

Platelet count $\geq 75 \times 10^9/L$

- For women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined non-hormonal contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 12 months after the last dose of rituximab or 18 months after the last dose of obinutuzumab

Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Non-vasectomized male patients must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 12 months after completing therapy with rituximab or 18 months after completing therapy with obinutuzumab.

A partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration

Total abstinence from sexual intercourse; double-barrier method (condom + diaphragm or cervical cup with spermicidal, contraceptive sponge, jellies, or cream)

Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Males must agree to abstain from sperm donation for at least 12 months after the last dose of rituximab or 18 months after the last obinutuzumab dose.

4.1.3 Exclusion Criteria

4.1.3.1 Patients Enrolled in the Dose-Finding Portion of the Study

Patients with MCL or SLL histology will be excluded from study entry.

4.1.3.2 Patients Enrolled in the Phase II Portion of the Study

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

- Patients with transformed lymphoma (*patients with discordant bone marrow involvement (i.e., low grade histology in bone marrow) may be considered after discussion with the Medical Monitor*)
- Prior therapy for NHL

4.1.3.3 All Patients

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

- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products

- Contraindication to receive any of the individual components of CHOP, rituximab, or obinutuzumab
- Prior anthracycline therapy
- Ongoing corticosteroid use >30 mg/day of prednisone or equivalent. Patients who received corticosteroid treatment with ≤30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to Cycle 1 Day 1. Patients may have received a brief (<7 days) course of systemic steroids (≤100 mg prednisone equivalent per day) prior to initiation of study therapy for control of lymphoma-related symptoms (See Section 4.4.1).
- CNS lymphoma *or primary mediastinal DLBCL*
- Vaccination with live vaccines within 28 days prior to treatment
- Chemotherapy or other investigational therapy within 28 days prior to the start of Cycle 1.
- History of other malignancy that could affect compliance with the protocol or interpretation of results

Patients with a history of curatively treated basal or squamous cell carcinoma or Stage 1 melanoma of the skin or in situ carcinoma of the cervix are eligible.

Patients with a malignancy that has been treated with surgery alone with curative intent will also be excluded, unless the malignancy has been in documented remission without treatment for ≥3 years prior to enrollment.

- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient, including renal disease that would preclude chemotherapy administration or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Significant CV disease (such as New York Heart Association Class III or IV cardiac disease, congestive heart failure, myocardial infarction within the past 6 months, unstable arrhythmias, or unstable angina) or significant pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Left ventricular ejection fraction <50% as defined by MUGA. Echocardiogram may be used if MUGA is not available.
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1
- Received the following agents within 7 days prior to the first dose of venetoclax:
 - Steroid therapy for anti-neoplastic intent within 7 days prior to *Cycle 1 Day 1*. See steroid use guidelines in Section 4.4.1 for specific exceptions.
 - Strong and moderate CYP3A inhibitors (see Appendix 5 for examples)
 - Strong and moderate CYP3A inducers (see Appendix 5 for examples)

Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within 3 days prior to the first dose of venetoclax.

- Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis
- Presence of positive test results for hepatitis B (HBcAb) or hepatitis C (hepatitis C virus [HCV]) antibody

Patients who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation

Patients with occult or prior HBV infection (defined as positive total HBcAb and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing.

- Known infection with HIV or human T-cell leukemia virus 1
- Women who are pregnant or lactating
- Recent major surgery (within 6 weeks prior to the start of Cycle 1 Day 1), other than for diagnosis
- Any of the following abnormal laboratory values:

Calculated estimated creatinine clearance (CRCL) < 50 mL/min with the use of the 24-hour creatinine clearance or modified Cockcroft-Gault equation (with the use of ideal body mass [IBM] instead of mass):

$$\text{CRCL} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [0.85 \text{ if female}]}{72 \cdot \text{serum creatinine (mg/dL)}}$$

Or, if serum creatinine is in $\mu\text{mol/L}$:

$$\text{CRCL} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine } (\mu\text{mol/L})}$$

AST or ALT > 2.5 × ULN (*unless due to disease involvement; Medical Monitor to be consulted prior to enrollment*)

Total bilirubin ≥ 1.5 × ULN (or > 3 × ULN for patients with documented Gilbert syndrome)

INR > 1.5 × ULN for patients not receiving therapeutic anticoagulation

PTT or aPTT > 1.5 × ULN

4.1.4 Criteria for Tumor Biopsy Tissue

- Eligible patients must have a representative formalin-fixed, paraffin-embedded tumor specimen to enable the definitive diagnosis of CD20-positive NHL/DLBCL available at the study site.

- The specimen must contain adequate evaluable tumor cells to enable Bcl-2 IHC and other relevant biomarker analysis.

Sample can be in a tissue block (preferred) or consist of 20 unstained serial slides, accompanied by an associated pathology report. If fewer than 20 unstained serial slides (accompanied by an associated pathology report) are available, then the study site should consult the Sponsor (or delegate) regarding the acceptability of a fewer number of slides. Cytological or fine-needle aspiration as well as bone marrow samples are not acceptable. In countries using a different fixative than formalin, available tissue block will be accepted and notation of the type of fixative should be included. In addition to slides in the Phase II portion of the study, a tissue punch for the construction of TMAs is required in patients who have an excisional biopsy sample available. If the archival tissue is unavailable or insufficient based on above criteria, the patient may still be eligible if the patient is willing to provide tissue from a pretreatment core or excisional/incisional biopsy of the tumor. Cytological or fine-needle aspiration samples are not acceptable. The sample should be shipped according to instructions provided in the laboratory manual. If a tissue block is provided, after necessary sections are cut and a core punch sample for TMA is taken, the remaining specimen will be returned to site.

Tissue samples must be sent to the central laboratory within 3 weeks of patient randomization.

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. Patients will be assigned to dose levels in the order in which they are enrolled. As described in Section 3.1, enrollment in the dose-finding portion of the study will be limited to patients with B-cell NHL with no prior R-CHOP therapy and who have received only a single prior treatment regimen.

In the Phase II portion of the study, previously untreated DLBCL with higher-risk clinical features as determined by an IPI score of 2–5 will be enrolled. Allocation to Arm A (venetoclax+R-CHOP) or Arm B (venetoclax+G-CHOP) will be by randomization if both arms are open to enrollment; allocation will otherwise be via direct assignment to the open arm. Randomization will be performed by an IxRS. Patients will be assigned in a 1:1 ratio to one of the two treatment arms until Arm B is filled, at which point all patients will be allocated to Arm A.

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. After the Sponsor reviews the documentation and approves the patient for enrollment, the Sponsor will provide the dose group assignment and the patient number will be assigned via the IxRS.

4.3 STUDY TREATMENT

4.3.1 Venetoclax

4.3.1.1 Formulation

The venetoclax tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Each bottle will be labeled per local regulatory requirements. A desiccant canister may be included in the bottle. The tablets must be stored at 15°C–25°C (59°F–77°F). If supplied with a desiccant, the desiccant canister should be returned to the bottle directly after each tablet removal.

For further details, see the ABT-199/GDC-0199 Investigator's Brochure.

4.3.1.2 Dosage, Administration, and Storage

Study patients will self-administer venetoclax tablets by mouth once daily (QD). Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or the patient's first meal of the day. *A meal containing approximately 30% of the total caloric content from fat is recommended to ensure adequate absorption of venetoclax.* On days that pre-dose PK sampling is required, *the patient's first meal of the day (e.g., breakfast) will be consumed in the morning at the clinic, and venetoclax dosing will occur in the clinic after completion of the to facilitate PK sampling.*

The recommended breakfast is as follows:

1 box cereal (30–40 g)

Skim milk (240 mL)

1 boiled egg

1 slice toast (15 g)

Margarine (10 g)

Total calories should be approximately 520 Kcal; 30% of the total caloric content of the meal is from fat. Total grams of fat should be approximately 17 grams.

See Section [3.1.2.1](#) for the venetoclax administration schedule.

On days when venetoclax plus R-CHOP or G-CHOP are given, the order of study treatment administration will be venetoclax prior to rituximab or obinutuzumab, and rituximab or obinutuzumab prior to CHOP (with the exception of the first dose of prednisone in each cycle; see Section [4.3.4](#)). On days when both venetoclax and prednisone are given, venetoclax will be taken prior to prednisone. If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be given and the second dose noted in the drug log. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible and ensure that the minimal interval between the current dose and the next dose is at least 16 hours in order

to avoid excessive drug accumulation after the next dose. Patients will be instructed to record the date and time they take their daily dose of venetoclax and prednisone. Diaries will be provided by the Sponsor for this purpose. Venetoclax must be stored according to labeled storage conditions.

All patients must receive prophylaxis for TLS (see Section 4.4.1.2) prior to the initiation of venetoclax plus R-CHOP or G-CHOP study treatment.

4.3.1.3 Dosage Delays and Modification

The dose of venetoclax should be withheld for clinically significant toxicity potentially related to venetoclax treatment (e.g., clinical TLS, febrile neutropenia) until the toxicity has resolved or improved to Grade ≤ 2 or $\geq 80\%$ of baseline. The dose of venetoclax may be reduced for Grade ≥ 3 toxicity or recurrent Grade ≥ 2 toxicity after consultation with the Medical Monitor (see Table 2).

4.3.2 Rituximab

4.3.2.1 Formulation

Rituximab (Rituxan[®]/MabThera[®]) is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in 100-mg (10 mL) and 500-mg (50 mL) single-use vials. The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, and 0.7 mg/mL polysorbate 80, after reconstitution with Sterile Water for Injection. The pH is adjusted to 6.5. Vials are for single use. Each vial and carton will contain a label (either single-panel or booklet) affixed to the vial or carton per individual country requirements.

4.3.2.2 Dosage, Administration, and Storage

Rituximab will be administered intravenously once per 21-day cycle in combination with CHOP for up to six cycles and as a single agent for two additional cycles. Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor. The infusion of 375 mg/m² will be based on the patient's body surface area (BSA) at screening and will remain the same throughout the study unless there is a > 10% change in body weight. On a given day, rituximab should be given after venetoclax and prior to CHOP (with the exception of the first dose of prednisone in each cycle; see Section 4.3.4).

See Section 3.1.2.1 for administration schedule in combination with CHOP.

Rituximab should not be administered as an IV push or bolus. IRRs may occur. Premedication consisting of acetaminophen, diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered beginning with the first infusion. Premedication may attenuate IRRs. Because transient hypotension may occur during

rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

4.3.2.2.1 First Infusion

The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If IRRs do not occur, the infusion rate should be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an IRR develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

4.3.2.2.2 Subsequent Infusions

If the patient tolerates the first infusion well, subsequent rituximab infusions may be administered at an initial rate of 100 mg/hr and increased in 100-mg/hr increments at 30-minute intervals to a maximum of 400 mg/hr, as tolerated or per an institution's standard of care IV administration procedure. If the patient does not tolerate the first infusion well, the guidelines for the first infusion should be followed.

Rituximab vials must be stored at 2°C–8°C (36°F–46°F). Rituximab vials should be stored in the outer carton in order to protect them from light. Rituximab solution for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours and has been shown to be stable for an additional 12 hours at room temperature. However, because rituximab does not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between rituximab and polyvinylchloride (PVC) or polyethylene bags have been observed.

See the local prescribing information for Rituxan/MabThera for additional information.

4.3.2.3 Dosage Modification

There will be no rituximab dose modification in this study. Patients who are at high risk for IRR or TLS complications (see Section 4.4.1.4) may, at the investigator's discretion, receive their initial dose of rituximab split over 2 consecutive days (e.g., 125 mg/m² on Cycle 1 Day 1, 250 mg/m² on Cycle 1 Day 2).

Any NCI CTCAE v4.0 toxicity Grade ≥ 3 in severity that is deemed related to rituximab treatment will require interruption of study treatment until resolution to Grade ≤ 1 . Resumption of rituximab treatment may be considered in patients with resolution of toxicities to Grade ≤ 2 within 3 weeks at the discretion of the investigator after consultation with the study Medical Monitor. Failure of such toxicities to resolve after 3 weeks of suspended study treatment will require permanent discontinuation of rituximab.

Patients who discontinue rituximab because of rituximab-related toxicity may continue to receive CHOP and/or venetoclax only after consultation by the investigator with the Medical Monitor.

4.3.3 Obinutuzumab

4.3.3.1 Formulation

Obinutuzumab is provided as a single-dose, sterile liquid formulation in a 50 mL pharmaceutical-grade glass vial containing a nominal 1000 mg of obinutuzumab (G3 material). The formulated drug product consists of 25 mg/mL drug substance (G3) formulated in histidine, trehalose, and poloxamer 188. The vial contains 41 mL (with 2.5% overfill).

For further details, see the Obinutuzumab Investigator's Brochure.

4.3.3.2 Handling and Storage

The recommended storage conditions for the obinutuzumab drug product are between 2°C and 8°C and protect from light. Chemical and physical in-use stability for obinutuzumab dilutions in 0.9% sodium chloride (NaCl) has been demonstrated for 24 hours at 2°C–8°C and at ambient temperature and ambient room lighting. The prepared diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C. Obinutuzumab should not be frozen or shaken. Mix gently. All transfer procedures require strict compliance with aseptic techniques. Do not use an additional in-line filter; this will avoid potential adsorption.

For further details, see the Obinutuzumab Investigator's Brochure.

4.3.3.3 Obinutuzumab Dose and Schedule

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg in combination with CHOP for up to six cycles and as a single agent for two additional cycles. Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor. On a given day, obinutuzumab should be given after venetoclax and prior to CHOP (with the exception of the first dose of prednisone in each cycle; see Section 4.3.4), and patients should be observed for 30 minutes prior to starting CHOP. Patients at high risk for IRR or TLS complications may, at the investigator's discretion, receive their obinutuzumab dose split over 2 consecutive days (e.g., 100 mg on Day 1, 900 mg on Day 2). During Cycle 1, obinutuzumab will also be administered on Days 8 and 15.

4.3.3.4 Obinutuzumab Preparation

Obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl to the final drug concentration of 4 mg/mL. With the use of a 250 mL infusion bag containing 0.9% NaCl, withdraw and

discard 40 mL of the sodium chloride. Withdraw 40 mL of obinutuzumab from a single glass vial and inject into the infusion bag (discard any unused portion of obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution; do not shake.

Administration sets with PVC, polyurethane, or polyethylene as product contact surfaces, and IV bags with polyolefin, polypropylene, PVC, or polyethylene as product contact surfaces are compatible and may be used.

4.3.3.5 Obinutuzumab Administration

Obinutuzumab should be administered to patients in a clinical setting (inpatient or outpatient), where full emergency resuscitation facilities are immediately available and patients should be under close supervision of the investigator at all times. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥ 2 hours in order to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, access (either through an IV line or central venous catheter) should remain in place for at least 1 hour from the end of infusion, and if no adverse events occur after 1 hour, the IV access may be removed.

See Section [4.4.1.4](#) and Section [4.4.1.5](#) for guidance on the use of premedication and prophylaxis of TLS prior to administration of obinutuzumab. Instructions for the first and subsequent infusions of obinutuzumab are presented in [Table 1](#).

Table 1 Administration of First and Subsequent Infusions of Obinutuzumab

First Infusion (Day 1)	Subsequent Infusions
<ul style="list-style-type: none"> • Begin infusion at and initial rate of 50 mg/hr. • If no infusion reaction occurs, increase the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. • If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred) if the reaction has resolved. 	<ul style="list-style-type: none"> • If a patient experienced an infusion reaction during the prior infusion, start at the same rate as the first infusion (50 mg/hr) and follow directions as noted. • If the patient tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of > 100 mg/hr), begin the infusion at a rate of 100 mg/hr. • If no infusion reaction occurs, increase the infusion rate in 100 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. • If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred) if the reaction has resolved.

Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus.

On days when both obinutuzumab and CHOP are given, obinutuzumab will be administered prior to CHOP (except for first dose of prednisone in each cycle; see Section 4.3.3.6) and patients should be observed for 30 minutes prior to starting CHOP. CHOP chemotherapy may be administered the next day if it cannot be given on the same day as obinutuzumab administration or if the obinutuzumab dose is split between 2 days. Prior to each obinutuzumab infusion that is given in combination with CHOP (Day 1 of Cycles 1–6), patients should take the Day 1 dose of oral prednisone (100 mg) specified for each cycle of the CHOP regimen. The prophylactic use of corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) may also be considered for patients thought to be at high risk for IRRs if deemed appropriate by the investigator and should be also administered prior to the obinutuzumab infusion.

For management of IRRs and anaphylaxis, see Section 4.3.3.8.

4.3.3.6 Premedication

Thirty to 60 minutes prior to all obinutuzumab infusions (following venetoclax dosing, if applicable), all of the following premedications will be given (unless contraindicated):

- Oral acetaminophen (650–1000 mg)

- An antihistamine, such as diphenhydramine (50–100 mg)
- Prior to each obinutuzumab infusion that is followed by CHOP chemotherapy, patients should take the Day 1 dose of prednisone (100 mg) specified for each cycle of the CHOP regimen.

The use of prophylactic corticosteroids (e.g., 100 mg IV prednisolone or equivalent) may also be considered for patients thought to be at high risk for IRRs and when deemed appropriate by the investigator; they should also be administered prior to the obinutuzumab infusion.

If the dose of obinutuzumab is split, the Day 2 dose of prednisone (100 mg) specified for each cycle of the CHOP regimen should be given prior to the infusion of obinutuzumab.

4.3.3.7 Management of Tumor Lysis Syndrome

For patients with evidence of TLS, obinutuzumab should be discontinued and the patients treated as clinically indicated. Following the complete resolution of TLS complications, obinutuzumab may be re-administered at the full dose during the next infusion in conjunction with prophylactic therapy as indicated (see Section [4.4.1.5](#)).

4.3.3.8 Management of Infusion-Related Reactions and Anaphylaxis

Medications (including epinephrine for SC injections, corticosteroids, diphenhydramine hydrochloride for IV injection) and resuscitation equipment should be available for immediate use at point of infusion. Management of infusion-related symptoms for obinutuzumab is summarized in [Table 2](#). In the event of a life-threatening IRR (that may include pulmonary or cardiac events) or an IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional drug should be administered. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from study treatment.

Patients who experience obinutuzumab-associated, infusion-related temperature elevations of $>38.5^{\circ}\text{C}$ or other minor infusion-related symptoms may be treated symptomatically with acetaminophen (≥ 500 mg) and/or H₁- and H₂-histamine-receptor antagonists (e.g., diphenhydramine hydrochloride, ranitidine). Serious infusion-related events, manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress, should be managed with additional supportive therapies (e.g., supplemental oxygen, β_2 -agonists, epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice.

Table 2 Management of Infusion-Related Symptoms

Infusion-Related Symptoms ^a	Guidance
Grades 1 and 2	Slow or withhold infusion. Give supportive treatment ^b . Upon symptom resolution, may resume infusion-rate escalation.
Grade 3	Discontinue infusion. Give supportive treatment ^b . Upon symptom resolution, may resume infusion rate escalation.
Grade 4	Discontinue infusion immediately, treat symptoms aggressively, and do not restart drug.

IV=intravenous.

^a Refer to National Cancer Institute Common Terminology Criteria for Adverse Events, (Version 4.0) for the grading of symptoms. This table does not refer to management of IgE-mediated allergic reactions, which should be managed as directed in Section 4.4.1.6.

^b Supportive treatment: Patients should be treated with acetaminophen and an antihistamine such as diphenhydramine hydrochloride if they have not been received in the previous 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg of IV prednisolone or equivalent), and/or bronchodilators. For hypotension, patients may require vasopressors.

4.3.3.9 Cardiac or Pulmonary Events

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

4.3.3.10 Dosage Modification or Delay

There will be no obinutuzumab dose modification in this study. See Section 4.3.6 and Table 3 for dose-delay guidelines.

4.3.4 CHOP Chemotherapy

4.3.4.1 Dosage and Administration

CHOP chemotherapy consists of IV cyclophosphamide, IV doxorubicin, vincristine administered by IV push, and oral prednisone or prednisolone. Standard CHOP will be administered for six 21-day cycles. Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor.

- Cyclophosphamide 750 mg/m² administered intravenously on Day 1
- Doxorubicin 50 mg/m² administered intravenously on Day 1
- Vincristine 1.4 mg/m² administered by IV push on Day 1 with a cap of 2.0 mg
- Prednisone 100 mg/day orally (PO) on Days 1–5

Note: The dose of prednisone follows the [National Comprehensive Cancer Network's recommendations \(2010\)](#) based on *Czuzman and colleagues (1999)*

and [Hiddemann and colleagues \(2005\)](#). Prednisone may be replaced with prednisolone (1:1 conversion, 100 mg) in countries where prednisone is not available or is not the therapy of choice.

The use of a taper of prednisone (or equivalent) after Day 5 is permitted when felt to be appropriate according to the investigator's standard practice.

CHO(P) will be administered according to the standard preparation and infusion procedures at each investigational site and after the rituximab or obinutuzumab infusion. Refer to the specific package inserts for preparation, administration, and storage guidelines.

On a given day, CHOP should be given after venetoclax plus rituximab or obinutuzumab, with the exception of the first dose of prednisone in each cycle, when prednisone is administered prior to the rituximab or obinutuzumab infusion. On all other days, when rituximab or obinutuzumab is not administered, prednisone is given as per institutional CHOP administration standard. Rituximab or obinutuzumab administration should be completed at least 30 minutes prior to administration of the CHO (cyclophosphamide, vincristine, and doxorubicin) infusions.

Cyclophosphamide, doxorubicin, and vincristine may be given on Day 2 of Cycle 1 if the rituximab or obinutuzumab dose is split or if the extended time of antibody administration does not permit dosing of first CHOP on the same day. If CHOP dosing is performed on Day 2 of Cycle 1, the first dose of venetoclax should be administered 3 days after CHOP (see Section [3.1.2.1](#)).

4.3.4.2 Dosage Modification or Delay

See Section [4.3.6](#) and [Table 3](#).

4.3.5 Administration of Granulocyte Colony-Stimulating Factor

All patients must receive G-CSF as primary prophylaxis for neutropenia starting with Cycle 1 and continuing through each additional cycle of *CHOP* therapy received.

4.3.6 Dosage Delays and Modifications

4.3.6.1 Dosage Delays and Modifications: Venetoclax, Rituximab, Obinutuzumab, and CHOP Chemotherapy

Guidelines for dose delay and modification of R/G-CHOP and venetoclax are shown in [Table 3](#). These guidelines pertain to dose delays and modifications based on physical examination findings, observed toxicities, and laboratory results obtained within 72 hours before study treatment administration. Dose delays and dose modifications as a result of adverse events not specified in [Table 2](#) should proceed on the basis of the principle of maintaining the dose intensity of R/G-CHOP. The determination of all dose and schedule modifications will be made on the basis of the investigator's assessment of ongoing clinical benefit with continuing study treatment in consultation with and with the approval of the Medical Monitor. It is recommended that blood counts be checked within

24–72 hours for patients with cytopenias resulting in dose delays to see if the counts have recovered.

No dose modifications of rituximab or obinutuzumab are allowed. Cyclophosphamide, doxorubicin, vincristine, and venetoclax doses may be re-escalated (even to the full dose) with the approval of the Medical Monitor.

If administration of chemotherapy is delayed, the administration of rituximab, obinutuzumab, and CHOP should be delayed for the same time frame; for example, if CHOP therapy is delayed, administration of rituximab should also be delayed so that they are given together beginning on Day 1 of the same cycle.

For non-hematologic toxicities, dosing of R-CHOP or G-CHOP may be resumed upon resolution to Grade ≤ 1 or baseline status. Resumption of dosing without complete resolution of toxicity may only be considered after careful weighing of the benefits and risks with the patient and agreement between the investigator and the Sponsor.

A dose delay of 14 days is permitted for R-CHOP or G-CHOP to allow recovery of hematologic toxicities to Grade ≤ 2 or non-hematologic toxicities to Grade ≤ 1 or baseline status for the first episode. Actions for recurrent hematologic adverse events are described in [Table 3](#). If treatment is delayed for more than 2 weeks (except for hepatitis B reactivation), the patient should be withdrawn from study treatment, except in exceptional circumstances requiring discussion with the Medical Monitor. (Note that lymphopenia is not considered a cytopenic toxicity, because it is an expected outcome of therapy) Patients who discontinue all study treatment for adverse events should remain in the study and continue to have disease assessments through progression and standard follow-up.

Table 3 Guidelines for Dose Delay or Modification of Venetoclax, Rituximab, or Obinutuzumab and CHOP Chemotherapy

Event(s)	Dose Delay or Modification
<p>Grade 3 or 4 neutropenia on Cycle Day 1 with or without infection or fever^a</p> <p>First delay</p> <p>Recurrent Grade 3 neutropenia on Cycle Day 1</p>	<ul style="list-style-type: none"> • Delay doses of all study treatment. • Administer growth factors; (e.g., G-CSF for neutropenia as indicated and for all subsequent cycles). • If ANC recovers to > 1000/μL by Day 7 of the scheduled date for the next cycle, administer full dose of study treatment. • If ANC recovers to > 1000/μL on or after Day 8 of the scheduled date for the next cycle, reduce the dose of venetoclax to the previously tested (lower) dose level (dose will be reduced by at least 25%). • If the primary cause of neutropenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of venetoclax. Decisions must be made in consultation with and with approval of the Medical Monitor. • Delay doses of all study treatment. • If ANC recovers to > 1000/μL by Day 7 of the scheduled date for the next cycle, administer full dose of study treatment. • If ANC recovers to > 1000/μL on or after Day 8 of the scheduled date for the next cycle, then: <ul style="list-style-type: none"> If no prior dose reduction of venetoclax: Reduce the dose of venetoclax to the previously tested (lower) dose level (dose will be reduced by \geq25%). If there was a prior reduction of venetoclax: the venetoclax dose reduction should be maintained, and the doses of cyclophosphamide and doxorubicin should be reduced to 75% of the original dose. For subsequent episodes, further dose reduction of venetoclax or doxorubicin and cyclophosphamide may be considered. • If Grade 3 neutropenia persists despite growth factor support and following venetoclax, cyclophosphamide and doxorubicin dose reductions, in the absence of fever, patient may continue with study treatment. • If patient develops Grade 3 febrile neutropenia or infection despite growth factor support and following venetoclax, cyclophosphamide and doxorubicin dose reductions, discontinue all study treatment permanently.

Table 3 Guidelines for Dose Delay or Modification of Venetoclax, Rituximab, or Obinutuzumab and CHOP Chemotherapy (cont.)

Event(s)	Dose Delay or Modification
Recurrent Grade 4 neutropenia on Cycle Day 1	<ul style="list-style-type: none"> • If patient develops persistent Grade 4 neutropenia requiring dose delay despite growth factor support and following venetoclax, cyclophosphamide and doxorubicin dose reductions, discontinue all study treatment permanently.
Febrile neutropenia or neutropenia with infection during Cycle 1	<ul style="list-style-type: none"> • Withhold obinutuzumab dose until it resolves. • If Cycle 1 Day 8 is delayed to within 2 days of Day 15, then omit the Day 8 dose and administer the Day 15 dose as previously scheduled (if infection or neutropenic fever has resolved). • If Cycle 1 Day 15 is delayed to within 2 days of Cycle 2, then omit the Day 15 dose and administer the Cycle 2 Day 1 dose of obinutuzumab+CHOP as scheduled (if infection or neutropenic fever has resolved).
Grade 4 thrombocytopenia, first episode	<ul style="list-style-type: none"> • Note: obinutuzumab should not be held for asymptomatic neutropenia. • Modify venetoclax dose by reducing to next dose level or decrease dosing schedule to 7 days
Recurrent Grade 3 thrombocytopenia in consecutive cycles	<ul style="list-style-type: none"> • Modify venetoclax dose by reducing to next dose level or decrease dosing schedule to 7 days • Delay doses of all study treatment.
Grade 3 thrombocytopenia on Cycle Day 1, first episode	<ul style="list-style-type: none"> • If platelet count recovers to > 50,000/μL by Day 7 of the scheduled date of the next cycle, administer full dose of study treatment. • If platelet count recovers to > 50,000/μL on or after Day 8 of the scheduled date of the next cycle, reduce the dose of venetoclax to the previously tested (lower) dose level (dose will be reduced by at least 25%) or decrease dosing schedule to 7 days. Full dose of R-CHOP or G-CHOP may be given. • If the patient had baseline thrombocytopenia and the primary cause of thrombocytopenia is thought to be lymphoma infiltration into the bone marrow, the investigator may elect not to reduce the dose of cyclophosphamide and doxorubicin.

Table 3 Guidelines for Dose Delay or Modification of Venetoclax, Rituximab, or Obinutuzumab and CHOP Chemotherapy (cont.)

Event(s)	Dose Delay or Modification
Recurrent Grade 3 or 4 thrombocytopenia on Cycle Day 1	<ul style="list-style-type: none"> • Delay doses of all study treatment. • Reduce the dose of venetoclax to the previously tested (lower) dose level (dose will be reduced by at least 25%) or decrease dosing schedule to 7 days. • If recurrent Grade 3 or 4 thrombocytopenia on Cycle Day 1 after venetoclax dose reduction The venetoclax dose reduction should be maintained, and the doses of cyclophosphamide and doxorubicin should be reduced to 75% of the original dose. For subsequent episodes, further dose reduction of venetoclax or doxorubicin and cyclophosphamide may be considered. • If patient develops Grade 4 thrombocytopenia following venetoclax, cyclophosphamide and doxorubicin dose reductions, discontinue all study treatment permanently.
Severe thrombocytopenia (platelets < 10,000/ μ L) and/or symptomatic bleeding in patients who are not receiving concomitant anticoagulants or platelet inhibitors during Cycle 1	<ul style="list-style-type: none"> • Withhold obinutuzumab in case of severe thrombocytopenia (platelets < 10,000/μL) or symptomatic bleeding (irrespective of platelet count) until it resolves. • If the Cycle 1 Day 8 dose is delayed, then omit the Day 8 dose and administer the Day 15 dose as previously scheduled (if symptomatic bleeding has resolved). • If the Cycle 1 Day 15 dose is delayed, then omit the Day 15 dose and administer the Cycle 2 Day 1 dose of obinutuzumab+CHOP as scheduled (if symptomatic bleeding has resolved).
Thrombocytopenia with platelets < 20,000/ μ L and/or symptomatic bleeding in patients who are receiving concomitant anticoagulants or platelet inhibitors during Cycle 1 ^{b, c}	<ul style="list-style-type: none"> • Withhold obinutuzumab in case of platelets < 20,000/μL or symptomatic bleeding (irrespective of platelet count) until it resolves. • If the Cycle 1 Day 8 dose is delayed, then omit the Day 8 dose and administer the Day 15 dose as previously scheduled (if symptomatic bleeding has resolved). • If the Cycle 1 Day 15 dose is delayed, then omit the Day 15 dose and administer the Cycle 2 Day 1 dose of obinutuzumab+CHOP as scheduled (if symptomatic bleeding has resolved). • For patients who are receiving concomitant anticoagulant when thrombocytopenia with platelets < 20,000/μL develops, adjust the dose or withhold the drug per investigator discretion. • For patients who are on platelet inhibitors when thrombocytopenia with platelets < 20,000/μL develops, consider temporarily withholding their use^c.
Grade 1 or 2 neutropenia and/or thrombocytopenia	<ul style="list-style-type: none"> • No dose reduction or delay

Table 3 Guidelines for Dose Delay or Modification of Venetoclax, Rituximab, or Obinutuzumab and CHOP Chemotherapy (cont.)

Event(s)	Dose Delay or Modification
Grade 3 or 4 infection, with or without neutropenia Hemorrhagic cystitis	<ul style="list-style-type: none"> Withhold rituximab or obinutuzumab. Patients should be adequately hydrated prior to and after cyclophosphamide administration and should be instructed to void frequently. If gross hematuria develops, cyclophosphamide should be withheld until resolution of cystitis. A dose reduction of 50% for cyclophosphamide may be considered at the next cycle. Re-escalation of cyclophosphamide to the initial full dose is recommended if symptoms do not recur.
Grade 1–4 heart failure or Grade 3 or 4 LVSD Bilirubin >3.0 mg/dL	<ul style="list-style-type: none"> Discontinue R-CHOP chemotherapy permanently. Delay treatment with R-CHOP until resolution to Grade ≤ 1 within 14 days. Evaluate for causality
Bilirubin between 1.5 and 3.0 mg/dL	<ul style="list-style-type: none"> Reduce doxorubicin and vincristine dose by 25% of baseline. With subsequent courses of treatment if bilirubin has returned to ≤ 1 mg/dL, full doses may be given. Give full dose of rituximab or obinutuzumab and continue current dose of cyclophosphamide and prednisone or prednisolone. Evaluate for causality.
Grade 4 neurotoxicity Grade 2 or 3 neurotoxicity	<ul style="list-style-type: none"> Discontinue R-CHOP or G-CHOP chemotherapy permanently. Withhold R- CHOP or G-CHOP chemotherapy. If recovered to Grade ≤ 1 value within 14 days, administer full dose rituximab and continue current dose of cyclophosphamide and prednisone or prednisolone. Reduce vincristine dose by 50% for current cycle and all subsequent cycles.
Grade 3 or 4 tumor lysis syndrome	<ul style="list-style-type: none"> Withhold all study treatment (venetoclax and R-CHOP). The patient’s next dose may be delayed for up to 14 days. See Section 4.6 and Appendix 6 for prophylaxis and management guidelines. Following complete resolution of TLS, obinutuzumab or rituximab may be re-administered at the full dose during next scheduled infusion, in conjunction with prophylactic therapy and CHOP chemotherapy. Venetoclax dosing may be reinitiated at target or reduced dose following discussion with the Medical Monitor, in conjunction with prophylactic therapy.
Anaphylaxis	<ul style="list-style-type: none"> Discontinue rituximab or obinutuzumab permanently. CHOP and venetoclax may be continued when recovered if not attributable to CHOP or venetoclax. Follow treatment guidelines in Section 4.3.3.8.
Grade 4 IRR	<ul style="list-style-type: none"> Discontinue rituximab or obinutuzumab permanently. CHOP and venetoclax may be continued when recovered. Follow treatment guidelines in Section 4.3.3.8.

Table 3 Guidelines for Dose Delay or Modification of Venetoclax, Rituximab, or Obinutuzumab and CHOP Chemotherapy (cont.)

Event(s)	Dose Delay or Modification
Grade 3 IRR, second episode	<ul style="list-style-type: none"> Discontinue rituximab or obinutuzumab permanently. CHOP and venetoclax may be continued when recovered. Follow treatment guidelines in Section 4.3.3.8.
Grade 1 neurotoxicity (peripheral neuropathy)	<ul style="list-style-type: none"> Continue treatment at full dose; vincristine may be decreased at the discretion of the investigator.
Grade 3 or 4 non-hematologic toxicity not specifically described above (excluding alopecia, nausea, and vomiting)	<ul style="list-style-type: none"> Delay R-CHOP or G-CHOP for a maximum of 2 weeks. If improved to Grade ≤ 1 or baseline, continue study therapy at full dose, or reduce dose at the discretion of the investigator per site's standard procedures after discussion with the Medical Monitor.
Grade 1 non-hematologic toxicity	<ul style="list-style-type: none"> No dose reduction or delay
Hepatitis B reactivation (as evidenced by new detectable HBV-DNA levels)	<ul style="list-style-type: none"> HBV-DNA levels detectable but ≤ 100 IU/mL: Re-test within 2 weeks. If still positive, withhold R-CHOP or G-CHOP and treat patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. HBV-DNA levels at WHO-recommended cutoff of > 100 IU/mL: withhold R-CHOP or G-CHOP and treat the patient with an appropriate nucleoside analogue. Immediately refer patient to a gastroenterologist or hepatologist. Rising HBV-DNA viral load while on an appropriate anti-viral therapy: Discontinue patient from rituximab or obinutuzumab and CHOP chemotherapy immediately.

CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone; G-CSF=granulocyte colony-stimulating factor; HBV=hepatitis B virus; IRR=infusion-related reaction; LMWH=low-molecular weight heparin; LVSD=left ventricular systolic dysfunction; R=rituximab; TLS=tumor lysis syndrome.

^a All on the basis of laboratory results obtained within the time frame listed in the schedule of assessments (see [Appendix 1](#)) prior to infusion of Day 1 of that cycle

^b If the clinical condition of the patient requires the use of concomitant anticoagulants, the patient is at increased risk of bleeding when thrombocytopenia with platelets $< 20,000/\mu\text{L}$ develops. When possible, replace prior therapy with vitamin K antagonists with LMWH before Cycle 1 Day 1.

^c Clinical decision-making may be adjusted depending on the patient-specific assessment of benefit and risk.

4.3.7 Permanent Treatment Discontinuation Criteria

Patients who experience toxicity that can be clearly attributed to any particular study drug treatment may discontinue treatment with the specific agent. If toxicity cannot be clearly attributed to a single agent and is considered possibly related to the combination treatment, treatment with multiple agents should be discontinued. Patients who discontinue treatment for reasons other than PD should remain in the study and continue to have disease assessments per protocol.

4.3.7.1 Permanent Treatment Discontinuation Criteria for Venetoclax

A patient should discontinue venetoclax permanently if any of the following occurs:

- Grade ≥ 3 toxicity that has a reasonable possibility of being related to the administration of venetoclax and that does not resolve to \leq Grade 2 within 3 weeks
- Recurrent Grade 4 neutropenia with infection and despite G-CSF support
- Disease progression
- Any dose delay of ≥ 4 weeks after last dose

Patients who discontinue venetoclax for reasons other than PD should remain on the study and continue to have disease assessments per the protocol. Patients may continue treatment with R-CHOP or G-CHOP only if it is determined to be in the best interests of the patient, after discussion between the investigators and Medical Monitor.

4.3.7.2 Permanent Treatment Discontinuation Criteria for Rituximab or Obinutuzumab

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

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

4.3.7.3 R-CHOP or G-CHOP Chemotherapy

Patients should discontinue protocol therapy for any dosing delay exceeding 14 days for the initiation of the next planned cycle of R-CHOP or G-CHOP. Any exceptions will require Sponsor approval.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening through 30 days after the last dose of venetoclax or CHOP, or 90 days after the last dose of rituximab or obinutuzumab, whichever is later. All

concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who are receiving oral contraceptives, stable doses of hormone replacement therapy, or other maintenance therapy should continue their use.

Steroid use not otherwise dictated by the protocol CHOP treatment will follow the guidelines outlined below:

- Corticosteroid use > 30 mg/day of prednisone or equivalent: Not allowed within 7 days prior to *Cycle 1 Day 1* except as specified below
- Corticosteroid use 15–30 mg/day of prednisone or equivalent: Must be documented to be on a stable dose of at least 4 weeks' duration prior to first dose of study drug.
- Corticosteroid use < 15 mg/day of prednisone or equivalent: Allowed

Exceptions to the above guidelines:

- Corticosteroid used for malignancy-related symptom control (up to 100 mg/day of prednisone or equivalent) prior to initiation of study treatment. Once study treatment has been given, corticosteroid use may be tapered down (must be \leq pre-study treatment dose) for no more than 5 days.
- Premedication for rituximab or obinutuzumab infusions, as indicated per protocol and/or site local practice (may replace dose of CHOP prednisone)
- Inhaled corticosteroids for the treatment of asthma or chronic obstructive pulmonary disease
- Topical steroids
- Replacement corticosteroid therapy for an inherited or acquired deficiency
- Steroid use to treat emergent issues not related to anti-neoplastic intent is allowed for no more than 7 days per event. For steroid treatment > 7 days, the Medical Monitor must be consulted to discuss allowing the patient to continue treatment.

4.4.1.1 CNS Prophylaxis

CNS prophylaxis with intrathecal chemotherapy may be given according to institutional practice and its use documented on the eCRF. CNS prophylaxis with systemic chemotherapy may be given only after completion of the primary response assessment (6–8 weeks after Day 1 of Cycle 8).

4.4.1.2 Prophylaxis for Hemorrhagic Cystitis

Patients should be adequately hydrated prior to and after cyclophosphamide administration and should be instructed to void frequently. Mesna may be used as prophylaxis according to institutional practice.

4.4.1.3 Treatment and Prophylaxis of Neutropenia

G-CSF should be administered as primary prophylaxis starting with Cycle 1 of therapy *and continue through each cycle of CHOP therapy received* for all patients unless there

is a medical contraindication or the investigator feels it is not in the patient's best interest to receive G-CSF.

4.4.1.4 Premedication before Rituximab or Obinutuzumab Therapy

Rituximab or obinutuzumab should not be administered as an IV push or bolus because IRRs may occur. Patients should be premedicated with acetaminophen/paracetamol and an antihistamine prior to all infusions of obinutuzumab. A single dose of prophylactic corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) may also be administered beginning with the first infusion, comprising the prednisone component of the CHOP treatment. Premedication may attenuate IRRs. Because transient hypotension may occur during rituximab or obinutuzumab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to infusion.

4.4.1.5 Prophylaxis for Tumor Lysis Syndrome

TLS is a risk for patients with NHL who are treated with high cell-killing agents. *The risk of TLS is a continuum based on multiple factors that include tumor burden and comorbidities. Risk is highest for those with bulky disease, elevated absolute lymphocyte count, elevated pretreatment LDH levels, compromised renal function, and dehydration. All patients should undergo tumor burden assessment and CBC with WBC differential, and blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine). Pre-existing chemistry abnormalities should be corrected prior to initiation of treatment with venetoclax.*

Patients who do not present with bulky disease are not considered at higher risk for TLS and do not require hospitalization, but may be hospitalized per discussion with the investigator and Medical Monitor.

The risk of TLS in the setting of R-CHOP or G-CHOP should be assessed by the investigator and prophylaxis and management undertaken per institutional standard.

All patients must receive prophylaxis for TLS prior to the initiation of the first dose of venetoclax. Prophylaxis will include the following:

- Appropriate hydration, consisting of a fluid intake of approximately 2–3 L/day starting 24–48 hours days prior to the start of venetoclax treatment and continued for at least 24 hours after the first dose (for patients for whom volume overload is considered a significant risk, hospitalization should be considered)
- Administration of an agent to reduce uric acid, such as allopurinol 300 mg/day, orally beginning 72 hours prior to the first venetoclax dose. Rasburicase IV should be administered (unless medically contraindicated) for those patients with elevated uric acid levels prior to treatment, which is defined as a value above the local laboratory ULN or 476 $\mu\text{mol/L}$. Agents should be given until normalization of serum uric acid and other laboratory evidence of TLS (e.g., elevated serum LDH levels).
- Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities prior to the first dose of

venetoclax, if abnormalities are observed, the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing.

- Patients at higher risk of TLS will be hospitalized for the initial venetoclax dose.
- For patients at particularly high risk for TLS, as judged by the investigator, consideration may be given to starting at a lower dose of venetoclax and increasing venetoclax dose in a stepwise fashion in discussion with the Medical Monitor.

On the day of the initial visit with administration of venetoclax (see Section 3.1.2.1), serial vital sign assessments will be performed, and serum chemistry and hematology samples will be drawn prior to the dose of venetoclax and at 8 and 24 hours following the dose (see Appendix 1). The serum chemistry and hematology samples will be immediately sent to the laboratory, and the investigator or designee must promptly review the results. Laboratory results from pre-dose samples must be reviewed prior to venetoclax administration unless laboratory results from within the prior 24 hours have already been reviewed. Laboratory values obtained prior to the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results from the 24-hour post-dose assessments must be reviewed prior to receiving the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 6.

4.4.1.5.1 Hospitalization

Patients exhibiting specific characteristics at screening or initiation of venetoclax treatment are considered to be at high risk for development of TLS and must be hospitalized for more intensive prophylaxis and monitored during the initial dose of venetoclax. These patients are identified by the presence of any of the following:

- Any lymph mass ≥ 10 cm on the screening CT scan
- Out-of-range (high) absolute lymphocyte count (ALC) or the presence of abnormal cells in the peripheral blood differential signifying circulating lymphoma cells

In addition to characteristics requiring mandatory hospitalization, other patient characteristics may suggest an increased risk of TLS. These include but are not limited to the following:

- Overall disease burden (e.g., several enlarged lymph nodes, even if none reaching 10 cm)
- Elevated LDH levels
- Compromised renal function, as evidenced by low CRCL
- Extensive bone marrow involvement
- Dehydration

Hospitalization is not mandatory for patients who exhibit these characteristics, but these and any other factors that are considered relevant to TLS should be considered in the

overall assessment of the patient's state and their risk to develop TLS. Investigators should use their judgment in their assessment of the patient's risk of TLS development and may choose to hospitalize any patient they consider to be at risk for the development of TLS during the first dose of venetoclax, with approval of the Medical Monitor.

Hospitalization will begin the evening prior to the first dose of venetoclax and continue for 24 hours after the first dose. Upon admission, serum chemistry and hematology laboratory samples should be drawn, and IV hydration should be started with a target of 150–200 mL/hr or as clinically appropriate. Laboratory results should be reviewed and electrolyte values should not demonstrate clinically significant abnormalities prior to the first dose of venetoclax, or the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing. A nephrologist (or acute dialysis service) must be consulted/contacted on hospital admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

Serial vital sign assessments will be performed, and TLS laboratory samples will be drawn (serum chemistry as defined in Section 4.5.1.5) prior to the first dose of venetoclax and at 8, 12, and 24 hours post-dose; additionally, hematology samples will be drawn at 8 and 24 hours post-dose (see Appendix 1). These samples are to be immediately sent to the laboratory and the investigator or designee must promptly review the results. Laboratory values obtained prior to the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results from the 24-hour post-dose sample must be reviewed prior to receiving the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 6.

4.4.1.6 Infection Prophylaxis

If clinically indicated, anti-infective prophylaxis for viral, fungal, bacterial, or pneumocystis infections is permitted. Although there is a potential for drug-drug interactions, there are likely to be limited potential clinical effects, therefore trimethoprim sulfamethoxazole can be considered for pneumocystis prophylaxis, with close clinical monitoring. The Medical Monitor should also be consulted regarding any consideration of the use of azoles as anti-fungal prophylaxis or therapy because of the potential for drug-drug interactions.

4.4.1.7 Monitoring and Treatment for Hepatitis B Reactivation

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

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

If the HBV-DNA assay becomes positive and is ≤ 100 IU/mL, the patient should be retested within 2 weeks. If the assay is still positive, treatment with R-CHOP or G-CHOP chemotherapy will be held and the patient should be treated with an appropriate nucleoside analogue (for at least 1 year after the last dose of rituximab or obinutuzumab) and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume R-CHOP or G-CHOP chemotherapy once the HBV-DNA levels decrease to undetectable levels.

If a patient's HBV-DNA level exceeds 100 IU/mL while the patient is receiving anti-viral medication, treatment with R-CHOP or G-CHOP will be permanently discontinued (see Section 4.3.6, Table 3).

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

4.4.1.8 Other Concomitant Medications

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (e.g., erythropoietin) if clinically indicated. G-CSF will be administered as primary prophylaxis in each cycle of *CHOP* therapy (see Section 4.4.1.3).

Anti-emetic therapy may be instituted for any patient if clinically indicated. It is recommended that CHOP infusions be administered following premedication with a serotonin (5-HT₃) antagonist (i.e., dolasetron, ondansetron, etc.) or per institutional practice.

Antidiarrheal therapy may be instituted for any patient if clinically indicated per institutional practice.

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment or at any time during study treatment. Systemic steroid therapy other than the prednisone component of CHOP will not be allowed during study treatment with the exceptions noted in Section 4.4.1.

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

4.4.2 Excluded Therapy

Patients who are discontinued from study treatment will be followed for safety outcomes for 30 days following the patient's last dose of venetoclax or CHOP (or 90 days following the patient's last dose of rituximab or obinutuzumab, whichever is later) or until the patient receives another anti-cancer therapy, whichever occurs first.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy. Supplemental systemic therapy for prophylaxis of CNS disease is permitted according to institutional practice only after primary response assessment and must be recorded in the eCRF.
- Radiotherapy prior to primary response assessment
- Immunotherapy
- Hormone therapy (other than contraceptives, hormone replacement therapy, or megestrol acetate)
- Any therapies intended for the treatment of lymphoma/leukemia whether FDA approved or experimental (outside of this study)
- Warfarin may be co-administered with venetoclax with caution and with the guidance of the Medical Monitor.

The following concomitant medications are not allowed from 7 days prior to the first dose of study drug and during venetoclax administration:

- Corticosteroid use > 30 mg/day of prednisone or equivalent (with some exceptions, see Section 4.4.1).
- Strong and moderate CYP3A4 inducers (see [Appendix 5](#) for examples)

The following concomitant medications are not allowed from 7 days prior to the administration of the first dose of study drug:

- Strong and moderate CYP3A inhibitors (see [Appendix 5](#) for examples)
- Strong and Moderate CYP3A inducers (see [Appendix 5](#) for examples)

Exclude strong and moderate CYP3A inhibitors through the DLT assessment period and consider alternative medications. If a patient requires use of these medications while he or she is receiving the target dose of venetoclax, once the DLT assessment period is complete, use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration.

After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.

- Exclude strong and moderate CYP3A inducers (see [Appendix 5](#) for examples) through the DLT assessment period and consider alternative medications. If a patient requires use of these medications while he or she is receiving the target

dose of venetoclax, once the DLT assessment is complete, use with caution and contact the Medical Monitor for guidance.

[Table 4](#) lists categories of excluded and cautionary medications.

A sample list of excluded medications and cautionary medications that fall into the categories within this section can be found in [Appendix 5](#). It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, refer to the appropriate product label.

Table 4 Excluded and Cautionary Medications

Excluded Medications
<p>Anti-cancer therapies including chemotherapy, radiotherapy, or other investigational therapy, including targeted small molecule agents:</p> <p style="padding-left: 40px;">Excluded 28 <i>days</i> prior to first dose and throughout venetoclax administration.</p> <p>Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent:</p> <p style="padding-left: 40px;">Excluded 8 weeks prior to first dose and throughout venetoclax administration</p> <p>Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit:</p> <p style="padding-left: 40px;">Excluded 3 days prior to first dose and throughout venetoclax administration</p>
Excluded through ramp-up and DLT assessment period (if applicable) and cautionary thereafter:
<p>Strong and Moderate CYP3A inhibitors:</p> <p style="padding-left: 40px;">Exclude through the DLT assessment period and consider alternative medications. If patient requires use of these medications while they are receiving the target dose of venetoclax, once the DLT assessment period is complete use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration.</p> <p style="padding-left: 40px;">After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.</p> <p>Strong and Moderate CYP3A inducers:</p> <p style="padding-left: 40px;">Exclude through the DLT assessment period and consider alternative medications. If patient requires use of these medications while they are receiving the target dose of venetoclax, use with caution and contact the Medical Monitor for guidance.</p>
Cautionary Medications
<p>Warfarin</p> <p>Weak CYP3A inducers</p> <p>Weak CYP3A inhibitors</p> <p>P-gp substrates</p> <p>BCRP substrates</p> <p>OATP1B1/1B3 substrates</p> <p>P-gp inhibitors</p> <p>BCRP inhibitors</p> <p>OATP1B1/B3 inhibitors</p>

DLT = dose-limiting toxicity.

Note: See [Appendix 5](#) for examples of these medications.

4.5 STUDY ASSESSMENTS

Please see [Appendix 1](#) for the schedule of assessments performed during the study.

4.5.1 Definitions of Study Assessments

4.5.1.1 Medical History and Demographics

Medical history includes all clinically significant diseases, smoking history, prior cancer history, prior cancer therapies and procedures, and all medications used by the patient from 7 days preceding the screening visit to Cycle 1 Day 1.

4.5.1.2 Vital Signs

Vital signs will include measurements of heart rate, systolic and diastolic blood pressure while the patient is in a seated position, temperature, weight, and BSA (screening only unless > 10% change in weight). Scheduled vital sign assessments should occur prior to drug dosing if applicable unless otherwise specified (see Section [4.4.1.5](#)).

4.5.1.3 Physical Examination

A complete physical examination should include the evaluation of head, eyes, ears, nose, and throat and CV, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

Targeted physical examinations (including weight) should be limited to systems of primary relevance (i.e., CV, respiratory, those associated with symptoms, and those associated with tumor assessment [lymph nodes, liver, and spleen]).

4.5.1.4 Tumor and Response Evaluation

All measurable disease must be documented at screening by a combined PET-CT scan *with a diagnostic quality CT component*. Response assessments will be determined by the investigator on the basis of imaging studies and bone marrow examinations (if appropriate), with the use of the modified Lugano Classification ([Cheson et al. 2014](#); see [Appendix 2](#)). *A five-point scale score is required as part of the PET scan response.* Responses will also be assessed by the IRC (see Section [3.7](#)).

Clinical response assessment should include evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly by physical examination.

Patients will be evaluated for disease response by PET-CT imaging after Cycle 4 and at 6 to 8 weeks after Day 1 of Cycle 8 *or last cycle received*. A bone marrow examination must be repeated to confirm a CR if *it was* previously positive, *if it was not performed*,

or if it was indeterminate at screening. For sites at which PET-CT is not available for interim assessment (after Cycle 4), diagnostic CT imaging is an acceptable alternative.

Diagnostic-quality CT scan with use of oral and IV contrast (unless medically contraindicated) must be obtained at baseline, *after Cycle 4* and at end of treatment evaluation (6 to 8 weeks after Day 1 of Cycle 8 *or last cycle received*). If PET-CT with diagnostic CT is not obtainable, a separate diagnostic CT scan must be performed at these timepoints in addition to the PET scans.

All patients who have not progressed will then be followed with clinical assessments every 3 months until progression or close of study, whichever occurs first. Assessments will be based on full physical examination. CT scans (with oral and IV contrast, unless medically contraindicated) will be performed every 6 months for 2 years and as clinically indicated *during these follow ups*. If a patient exhibits clinical signs of possible disease progression (i.e., increased or de novo enlargement of liver, spleen or lymph nodes on physical examination), additional assessments including PET-CT or contrast-enhanced CT scan and/or bone marrow must be performed to evaluate for PD.

CT scans (with contrast) should include chest, abdomen, and pelvis scans; CT scans of the neck should be included if clinically indicated (*MRIs may be used instead of CT scans in patients for whom CT scans are contraindicated*). CT scans for response assessment may be limited to areas of prior involvement only if required by local regulatory authorities.

Bone marrow examinations should include biopsy and/or aspirate for morphology and flow cytometry and are required at screening.

4.5.1.5 Laboratory Assessments

On days of study drug administration, pre-dose laboratory samples should be drawn within 0–4 hours before the start of treatment, unless otherwise specified. Cycle 1 Day 1 local laboratory assessments can be performed on Day -1 if this schedule is preferable to the site. Instruction manuals and supply kits will be provided for all central laboratory assessments.

4.5.1.5.1 Central Laboratory Assessments

Samples for the following assessments will be sent to one or several laboratories or to the Sponsor for analyses.

- Lymphocyte subset counts. Whole blood samples will be analyzed by flow cytometry for B cells (CD19⁺), T-cell subsets (CD3⁺, CD4⁺, CD8⁺), and NK cells (CD16⁺, CD56⁺)
- Hepatitis B DNA levels (when appropriate)

Monitoring of HBV-DNA levels is mandatory for patients who are positive for HBcAb and enter the study with negative titers. For instructions on the management of these patients, see Section [4.4.1.7](#).

- PK assays

Serum samples will be obtained for measurement of *rituximab* or obinutuzumab concentrations and EDTA-anticoagulated; plasma samples will be obtained for measurement of venetoclax or *CHOP* concentrations at timepoints noted in [Appendix 3](#). *The samples will be sent to the central laboratory and then to a Sponsor designated bioanalytical laboratory or to the Sponsor or designee for analysis. Relevant biotransformation products of study treatment may also be analyzed at the discretion of the Sponsor.*
- Blood and tumor tissue (tumor biopsy) for *BCL2* family expression (by IHC), copy number alteration and translocation status (by FISH), DLBCL prognostic markers, and other DLBCL disease biology markers including resistance markers.
- Peripheral blood for MRD assessments

4.5.1.5.2 Local Laboratory Assessments

Samples for hematology, serum chemistry, liver function, and pregnancy will be analyzed at the study site's local laboratory.

- Hematology: complete blood count (hemoglobin, hematocrit, RBC count, and WBC count), platelet count, ANC, absolute lymphocyte count, and percent or absolute differential counts)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, magnesium, phosphorus, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, and uric acid
- Viral serology and detection
 - Hepatitis B (HBsAg and HBcAb)
 - HCV antibody (also HCV RNA by PCR if the patient is HCV antibody positive)
- Serum pregnancy test in females of childbearing potential

4.5.1.6 Electrocardiogram

A 12-lead ECG is required at screening and as clinically indicated. ECGs for each patient should be obtained with use of the same machine when possible. ECGs should be obtained in triplicate.

4.5.1.7 MUGA/Echocardiogram

MUGA scans will be obtained prior to treatment (see [Appendix 1](#)). Echocardiogram may be used if MUGA is not available. Any clinically significant changes in cardiac function must be reported within 7 days.

4.5.2 Screening and Pretreatment Assessments

All screening evaluations must be completed and reviewed by the Medical Monitor or designee to confirm that patients meet eligibility criteria and are approved for enrollment before the first dose of study drug. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or

evaluations. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site.

Screening and pretreatment tests and evaluations will be performed within 21 days preceding the first dose of study drug (except PET-CT scan, which may be performed up to 28 days preceding the first dose of study drug, providing no anti-tumor therapy was administered in this period). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 21 days prior to first dose of study drug may be used (bone marrow examination could have been performed up to 3 months prior to Cycle 1 Day 1); such tests do not need to be repeated for screening.

See the Schedule of Assessments provided in [Appendix 1](#) for the schedule of screening and pretreatment assessments.

4.5.3 Roche Clinical Repository

4.5.3.1 Overview of the Roche Clinical Repository

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

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

- 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

4.5.3.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section [4.5.3](#)) will not be applicable at that site.

4.5.3.3 Sample Collection

The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Tissue and blood samples will be collected and sent to the central laboratories as part of the planned study assessments. Any samples at the central laboratories, except PK samples, that remain from the planned study assessments may be taken and sent to the RCR if the patient consents to the optional RCR sampling.

The following samples will be collected for identification of genetic (inherited) biomarkers:

- One whole blood sample for DNA extraction will be drawn at baseline.

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 Sample Handling and Logistics 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).

The dynamic biomarker specimens for DNA analysis will be subject to the confidentiality standards described below.

4.5.3.4 Confidentiality

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

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties 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 derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy regarding study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.3.5 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 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.

4.5.3.6 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 with the 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 GO27878 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 GO27878.

4.5.3.7 Monitoring and Oversight

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

monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.5.4 Assessments during Treatment

All visits must occur within ± 1 day from the scheduled date, unless otherwise noted. All assessments will be performed on the day of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration of each cycle should be performed prior to study drug infusion, unless otherwise noted.

See the Schedule of Assessments provided in [Appendix 1](#) for the schedule of treatment period assessments.

4.5.5 End of Treatment Visit

Patients who complete the study treatment period (defined as eight cycles) or who discontinue early will have an End of Treatment Visit, 6 to 8 weeks from Day 1 of the last cycle received.

The visit at which response assessment shows PD may be used as the End of Treatment Visit.

See the Schedule of Assessments provided in [Appendix 1](#) for assessments to be performed.

4.5.6 Follow-Up Assessments

Ongoing adverse events thought to be related to venetoclax, CHOP, rituximab, or obinutuzumab will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-tumor treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or when it has been determined that the study treatment or participation is not the cause of the adverse event.

Patients will be followed for response until disease progression, death, or study closure, whichever occurs first.

4.5.7 Survival Follow-Up Assessments

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until death, lost to follow-up, consent withdrawal, or study termination by Roche, whichever occurs first. All patients will be followed for survival and new anti-lymphoma therapy information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the investigator), is lost to follow-up, dies, or the study is terminated by the Sponsor, whichever occurs first. If the patient withdraws from the study, the study staff may use a public information source

(e.g., county records) to obtain information about survival status only if permitted per local regulations.

Study closure will occur approximately 2 years after the last patient has completed treatment.

See the Schedule of Assessments provided in [Appendix 1](#) for specified follow-up assessments.

4.6 PATIENT DISCONTINUATION

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

See Section [4.3.7](#) for treatment discontinuation criteria.

See [Appendix 1](#) for assessments that are to be performed for patients who prematurely withdraw from the study.

4.7 STUDY DISCONTINUATION

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of F. Hoffmann-La Roche Ltd. In addition, F. Hoffmann-La Roche Ltd retains the right to discontinue development of venetoclax in combination with Rituximab or Obinutuzumab and CHOP at any time. F. Hoffmann-La Roche Ltd reserves the right to discontinue the trial prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating subjects within 1 week. As directed by F. Hoffmann-La Roche Ltd, all trial materials must be collected and all CRFs completed to the greatest extent possible.

4.8 POST-STUDY ACCESS TO VENETOCLAX, OBINUTUZUMAB, AND RITUXIMAB

The Sponsor will offer post-study access to the study drug (venetoclax, obinutuzumab, and rituximab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being*
- There are no appropriate alternative treatments available to the patient*
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them*

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)*
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for NHL/DLBCL*
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for NHL/DLBCL*
- Provision of study drug is not permitted under the laws and regulations of the patient's country*

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

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

4.9 ASSAY METHODS

Rituximab and obinutuzumab serum concentrations will be measured using a validated ELISA method. Plasma concentrations of venetoclax will be measured using a validated liquid chromatography tandem mass spectrometry method. The CHO components of CHOP may be measured in plasma if needed to confirm exposure for these three chemotherapy drugs. Plasma concentrations of prednisone will be measured if needed to test for a potential effect of venetoclax on prednisone pharmacokinetics. Bcl-2 and other exploratory markers will be evaluated from lymph node tissue with use of validated IHC, FISH, quantitative real-time PCR, and sequencing methodologies.

4.10 STATISTICAL METHODS

The final analysis will be based on patient data collected through study discontinuation. Analyses will be based on treated patients (i.e., patients who have received any amount of R/G-CHOP or venetoclax). Analyses will be provided separately for the dose-finding and extension cohorts where appropriate. Data from patients who receive R-CHOP or G-CHOP only (i.e., have not received any venetoclax), will be summarized separately.

4.10.1 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and discontinuations from the study will be summarized separately for the dose-finding and extension cohorts where appropriate.

Demographic and baseline characteristics, such as age, sex, race/ethnicity, and type and duration of malignancy will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables.

This study is not designed to detect sex-specific differences. There is no existing clinical data to suggest sex-specific differences regarding efficacy or safety of the investigational drugs. Therefore, a specific male/female distribution is not defined for the study. Males and females are equally eligible to participate if they meet all the inclusion criteria and none of the exclusion criteria.

Study drug administration data will be listed by dose level and line of therapy and any dose modifications will be flagged. The number of doses, treatment cycles, and average dose received for venetoclax plus R-CHOP or G-CHOP for the schedule/cohort will be summarized by cohort and dose level with the use of means, SDs, medians, and ranges.

4.10.2 Safety Analyses

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

All recorded adverse event data will be listed by line of therapy, study site, patient number, and schedule/cohort. All adverse events occurring on or after first study treatment will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade. All serious adverse events will be listed separately and summarized.

Incidence and nature of DLTs experienced within the combination DLT assessment window will be listed by dose cohort and study arm. Patients who withdraw from study treatment prior to completing the DLT assessment window for reasons other than DLT will be considered un-evaluable for DLT and MTD assessments and will be replaced.

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

Relevant laboratory and vital sign (temperature, heart rate, respiratory rate, and blood pressure) data will be displayed by time, with NCI CTCAE v4.0 Grade 3 and 4 values identified where appropriate.

4.10.3 Pharmacokinetic and Pharmacodynamic Analyses

Mean serum and plasma concentrations, as appropriate, of venetoclax, rituximab, obinutuzumab, and CHOP components versus time will be tabulated and plotted, and

summary statistics will be computed for each scheduled sampling time after appropriate grouping. Concentration-time data for venetoclax and the other analytes will be analyzed using non-compartmental methods, and the PK parameters will be grouped and summarized as appropriate.

Additional analyses, such as population PK/pharmacodynamic analysis, may be performed to characterize the pharmacokinetics and potential correlations of exposure with dose, demographics, pharmacodynamic, safety, and efficacy outcomes. The results of such 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 study treatment.

4.10.4 Activity Analyses

4.10.4.1 Tumor Assessment Data

All patients in the extension cohort who receive any amount of venetoclax or R-CHOP/G-CHOP will be included in the activity analysis.

Response assessment (CR, PR, etc.) as assessed by investigator and central review (IRC) by both CT and by combined PET-CT imaging will be summarized. Summaries will be provided across all patients, by Bcl-2 and c-Myc status and molecular subtype. Cross-tabulations with IPI score will be provided as exploratory analyses, provided that enough patients are available within cells. DOR and PFS will be summarized. An exploratory analysis of response will be provided on the subset of patients who receive six cycles of CHOP.

Response assessment is determined using the modified Lugano Classification: Revised Criteria for Response Assessment ([Cheson et al. 2014](#)) specified in [Appendix 2](#). Among patients with an OR, DOR will be defined as the time from the initial CR or PR to the time of disease progression or death. If a patient does not experience death or disease progression before the end of the study, DOR will be censored at the day of the last tumor assessment.

PFS is defined as the time from the first day of study treatment to disease progression or death while enrolled in the study (defined as death from any cause within 12 weeks of last tumor assessment). If a patient has not experienced PD or death, PFS will be censored at the day of the last tumor assessment.

4.10.4.2 Interim Analyses

Interim analyses will be incorporated into the Phase II portion of the study in order to guide potential early stopping of enrollment in the event of lower than expected CR rate. Data from completed and ongoing studies using R-CHOP and/or G-CHOP will be used as historical controls for comparison. Currently available data indicates that the historical CR rate based on CT is 65% for Bcl-2 high patients and 72% for Bcl-2 low patients. Historical PET-defined CR rates for each of the four biological subgroups are

expected to be available from ongoing studies for comparison by the time of first interim analysis. *An extension of the predictive probability design (Lee and Liu 2008)* will be used to guide stopping by comparing CR rates in the venetoclax+R-CHOP arm with historical controls using R-CHOP. If at any time, interim analysis suggests that the CR rate is lower than expected, the IMC and SOC will review the data and decide whether to recommend stopping enrollment. Interim analysis decision rules will be provided in the Statistical Analysis Plan, and will use the most current historical control data available at the time of analysis.

Additional analyses will be incorporated into the Phase II portion of the study in order to evaluate the safety and tolerability of the recommended Phase II dose of venetoclax and to guide early stopping of enrollment, a decrease of dose or dosing schedule for safety reasons on the basis of toxicities observed and ability to maintain chemotherapy dose intensity.

4.10.4.3 Predictive Diagnostics

Assay results of additional markers beyond Bcl-2, c-Myc, and molecular subtype may be explored and may be reported by response status.

4.10.5 Exploratory Analyses

The effects of demographic and baseline prognostic characteristics, including *BCL2* copy number gain and expression of transcripts for *BCL2* and family members, other apoptotic genes, and genes associated with the ABC or GCB subtypes of DLBCL on efficacy outcomes) will be evaluated using univariate and/or multivariate statistical methods such as Cox regression and logistic regression.

4.10.6 Determination of Sample Size

The sample size for the dose-finding stage is based on a modified 3+3 design in order to guide dose and schedule selection for the Phase II portion on the basis of DLTs. The expected enrollment for the dose-finding stage is 3–6 patients per dose level in each of the R-CHOP+venetoclax and G-CHOP+venetoclax arms.

The sample size for the R-CHOP+venetoclax arm in Phase II is based on obtaining a sufficient number for estimation of PET-negative CR rate in patients with *DE* (Bcl-2 and c-Myc co-expressing) DLBCL, overall, for Bcl-2 high patients, and within each of four mutually exclusive biological subgroups: Bcl-2 high and ABC, Bcl-2 high and GCB, Bcl-2 low and ABC, and Bcl-2 low and GCB. The expected enrollment for the R-CHOP+venetoclax arm in Phase II is approximately 160–200 patients in order to enroll approximately 50 *DE*-DLBCL patients, approximately 80–100 Bcl-2 high patients, and approximately 40–50 patients in each of the two Bcl-2 high subgroups. With 50 patients, 95% confidence intervals for estimation of CR would have a margin of error not exceeding 16%. The margin of error would decrease to 9% with 150 patients and to 8% with 200 patients. [Table 5](#) shows Clopper and Pearson 95% CIs for expected observed rates for sample sizes of 50, 100, 150, and 200.

Table 5 95% Confidence Intervals for Expected Observed Rates for Sample Sizes

R-CHOP+ venetoclax CR rate	50 patients #CR (CI for rate)	100 patients #CR (CI for rate)	150 patients #CR (CI for rate)	200 patients #CR (CI for rate)
80%	40 (66%, 90%)	80 (71%, 87%)	120 (73%, 86%)	160 (73%, 86%)
75%	37 (60%, 85%)	75 (65%, 83%)	112 (67%, 81%)	150 (68%, 81%)
70%	35 (55%, 82%)	70 (60%, 79%)	105 (62%, 77%)	140 (62%, 77%)
65%	32 (49%, 77%)	65 (55%, 74%)	97 (56%, 72%)	130 (57%, 72%)

CR=complete response; CI=confidence interval (Clopper and Pearson 95%);
CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone; R=rituximab.

4.11 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 with 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 will be sent directly to the Sponsor through use of 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 Sponsor's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor as outlined in Section 5.3.

5.1.1 Adverse Event

According to the ICH Guidelines for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product regardless of causal attribution. Therefore, an adverse event can 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 [5.2.5.10](#)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.1.2 Serious Adverse Event (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 might have caused death had it occurred in a more severe form or was allowed to continue.
- Requires or prolongs inpatient hospitalization (see Section [5.2.5.11](#))
- Results in persistent or significant disability and/or incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v4.0 criteria; see Section [5.2.3](#)); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

“Serious” is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

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 *via the Adverse Event eCRF* (i.e., no more than 24 hours after learning of the event; see Section 5.3.2 for reporting instructions).

5.1.3 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 *via the Adverse Event eCRF* (i.e., no more than 24 hours after learning of the event; see Section 5.3.2 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 5.2.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below
Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study drug is suspected.
- Grade 4 febrile neutropenia
- Grade ≥ 3 IRRs to rituximab or obinutuzumab
- Grade ≥ 4 TLS

Hepatitis B reactivation will be followed as an adverse event of particular interest.

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.3, Section 5.4, and Section 5.5.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity (see Section 5.2.3), and causality (see Section 5.2.4).

5.2.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.3.2 for instructions for reporting serious adverse events).

After initiation of study medications (venetoclax, rituximab, obinutuzumab, or CHOP), all adverse events, regardless of relationship to study drug, will be reported through 30 days after the last dose of venetoclax or CHOP, or 90 days after the last dose of rituximab or obinutuzumab, whichever is later. After this period, the investigator should report any *deaths*, serious adverse events or adverse events of special interest that are believed to be related to prior study drug treatment (see Section 5.5).

5.2.2 Eliciting Adverse Events

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:

“How have you felt since your last clinic visit?”

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

5.2.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 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 one's self, 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 5.3.2 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

^d Grade 4 and 5 events must be reported as serious adverse events (see Section 5.3.2 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

5.2.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see Table 7):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the adverse event follows a known pattern of response to the study drug, and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction, and if applicable, reappears upon rechallenge.
NO	<u>Adverse events will be considered related, unless they fulfill the criteria as specified below:</u> Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication) and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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

5.2.5 Procedures for Recording Adverse Events

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

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

5.2.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and that are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction [IRR]") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated IRR eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated IRR eCRF.

5.2.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than IRRs (see Section 5.2.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each

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

5.2.5.3 Adverse Events Occurring Secondary to Other Events

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

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

5.2.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded at the time the event is first reported, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this, and the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.3.2 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.

5.2.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.2.5.4 for details on recording persistent adverse events).

5.2.5.6 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.2.5.4 for details on recording persistent adverse events).

5.2.5.7 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ 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 5.2.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.3.2).

5.2.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.2.1) that are attributed by the investigator solely to progression of lymphoma should be recorded only on the Study Completion/Early Discontinuation eCRF. All other deaths on the study, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.3.2).

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. The term "**sudden death**" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or

without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. 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.

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

5.2.5.9 Preexisting Medical Conditions

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

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

5.2.5.10 Lack of Efficacy or Worsening of Lymphoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the modified Lugano Classification: Revised Criteria for Response Assessment (see [Appendix 2](#)). In rare cases, the determination of clinical progression will be on the basis of symptomatic deterioration. However, every effort should be made to document progression with the use of objective criteria. If there is any uncertainty as to whether an event is the result of disease progression, it should be reported as an adverse event.

5.2.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient 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 [5.1.2](#)), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- *Planned hospitalization* required by the protocol (e.g., to provide TLS prophylaxis or monitoring without significant clinical sequelae, or to perform an efficacy measurement for the study)
- Hospitalization for respite care

- 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

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

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

5.2.5.12 Adverse Events Associated with an Overdose or Error in Drug 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 may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.3.2).

5.3 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 *via the Adverse Event eCRF*; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately *via the Adverse Event eCRF* (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.

5.3.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information (North America)

Medical Monitor: [REDACTED], M.D.

Telephone Number: [REDACTED]

Alternate Telephone Number: (888) 835-2555

[REDACTED] Medical Responsible Contact Information (Rest of World)

Medical Advisor (based in Spain): [REDACTED], M.D.

Telephone Number: [REDACTED]

Medical Advisor (based in Singapore): [REDACTED], M.D.

Telephone Number: [REDACTED]

Medical Emergency Contact Center: [REDACTED]

Alternate Telephone Number: [REDACTED]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

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

5.3.2.1 Events Occurring prior to Initiation of Study Drug

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). The Serious Adverse Event/Adverse Event of Special Interest Reporting Form can also be scanned and e-mailed.

5.3.2.2 Events Occurring after Initiation of Study Drug

After initiation of study drug, serious adverse events and adverse events of special interest will be reported through 30 days after the last dose of venetoclax or CHOP or

90 days after the last dose of rituximab or obinutuzumab, whichever is later. 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 EDC system. A report will be generated and sent to Roche Safety Risk Management or its designee by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form and fax cover sheet should be completed and faxed *or scanned and emailed* to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). After 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 [5.5](#).

5.3.3 Reporting Requirements for Pregnancies

5.3.3.1 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 12 months after the last dose of venetoclax or rituximab or within 18 months after the last dose of obinutuzumab, whichever is later. A Pregnancy eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue through 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 update the Pregnancy eCRF when updated information on the course and outcome of the pregnancy becomes available.

In the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed *or scanned and emailed* to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy) with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.3.3.2 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 12 months after the last dose of venetoclax or rituximab or within 18 months after the last dose of obinutuzumab, whichever is later. A Pregnancy eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section [5.3.3.1](#).

5.3.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.3.2](#)).

5.3.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as 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 [5.3.2](#)).

5.4 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.4.1 Investigator Follow-Up

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

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

verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.3.3.1.

5.4.2 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.

5.5 POST-STUDY ADVERSE EVENTS

At the time of *study treatment* completion or *study treatment* discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The Sponsor should be notified if the investigator becomes aware of any serious adverse event or adverse event of special interest that occurs after the end of the adverse event reporting period (defined as 30 days after the last dose of venetoclax or CHOP or 90 days after the last dose of rituximab or obinutuzumab, whichever is later [see Section 5.2.1]) if the event is believed to be related to prior study drug treatment. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug or the female partner of a male patient exposed to study drug.

The investigator should report these events directly to Roche Safety Risk Management via telephone or via fax machine *or scanned and emailed* with the use the Serious Adverse Event/Adverse Event of Special Interest Reporting Form and fax cover sheet (see "Protocol Administrative and Contact Information & List of Investigators").

5.6 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 on the basis of applicable legislation.

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

- ABT-199/GDC-0199 Investigator's Brochure
- Obinutuzumab Investigator's Brochure
- Local prescribing information for rituximab

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. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with the Sponsor or the Sponsor's representative:

- FDA Form 1572 for each site (for all studies conducted under IND regulations), signed by the Principal Investigator
 - The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae and evidence of licensure of the Principal Investigator and all subinvestigators
- Complete financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572
- Federalwide Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form
 - The Sponsor or its designee must review any proposed deviations from the sample Informed Consent Form.
- Current laboratory certification of the laboratory performing the analysis (if other than a Sponsor-approved central laboratory), and current reference ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator's Brochure Receipt signed and dated by the Principal Investigator

- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable), IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator
- Canada only when applicable: original Qualified Investigator Undertaking Form, signed by each Canadian investigator involved in the study

6.2 STUDY COMPLETION

The following data and materials are required by Roche before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (i.e., other than Sponsor-approved central laboratory) and current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and subinvestigator, FDA Form 1572 for each site)
- A signed and dated Protocol Amendment Acceptance Form(s) [if applicable]
- Updated financial disclosure forms for the Principal Investigator and all subinvestigators listed on the FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

6.3 INFORMED CONSENT FORM

The Sponsor's Sample Informed Consent Form will be provided to each site. The Sponsor or its designee must review and approve any proposed deviations from the Sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB/EC-approved Consent Forms must be provided to Sponsor for regulatory purposes.

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

was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to the Sponsor for regulatory purposes.

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

6.3.1 Optional Research Informed Consent

If archival tissue and/or plasma/serum collection for optional research described in Section 4.5.3 is approved by the IRB/IEC, the Consent Form entitled "Sample Research Informed Consent Form" will be provided by the Sponsor to each study site. This form gives patients the option to authorize the collection and use of these samples and personal health information for additional research purposes. Signing of this separate consent form is not required for enrollment in the trial but is required prior to any optional research sample collection. All procedures outlined above for review, approval, processing, and use of Consent Forms also apply to this optional research form.

In the United States, each Informed Consent Form may also include authorization allowing the institution, investigator, subinvestigator, and the Sponsor(s) to use and disclose Personal Health information in compliance with the HIPAA of 1996.

Signed and dated Informed Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

6.4 COMMUNICATION WITH THE 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 for review and approval 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 regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined adverse events to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all serious adverse events, whereas others require notification only of events that are serious, assessed to be related to study treatment, and are unexpected. 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 regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's Study File.

6.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Sponsor representative to inspect study data, patients' medical records, and eCRFs. The Principal Investigator will permit Sponsor monitors/representatives and collaborators, the FDA, other regulatory agencies, IRBs, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.6 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using 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.

6.7 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 the pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

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.

6.8 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 (for clinical research purposes) would be one that: 1) allows data entry only by authorized individuals, 2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file), 3) protects the database from tampering, and 4) ensures data preservation.

In collaboration with the study monitor, the Sponsor's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

6.9 STUDY MEDICATION ACCOUNTABILITY

All study drugs required for completion of this study will be provided by the Sponsor. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

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

Study drugs 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, as determined by the study site. If the study site chooses to destroy the study drug, the method of destruction must be documented.

The Sponsor must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.10 DISCLOSURE OF DATA

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 to use and disclose personal health information) signed by the patient or 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 regulatory agencies, national and local health authorities, the Sponsor monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

6.11 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of investigational medicinal product, 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.

7. REFERENCES

- Ackler S, Mitten MJ, Foster K, et al. The Bcl-2 inhibitor ABT-263 enhances the response of multiple chemotherapeutic regimens in hematologic tumors in vivo. *Cancer Chemother Pharmacol* 2010;66:869–80.
- Advani RH, Chen H, Habermann TM, et al. Comparison of conventional prognostic indices in patients older than 60 years with diffuse large B-cell lymphoma treated with R-CHOP in the US Intergroup Study (ECOG 4494, CALGB 9793): consideration of age greater than 70 years in an elderly prognostic index (E-IPI). *Br J Haematol* 2010;151:143–51.
- American Cancer Society. *Cancer Facts & Figures*. Atlanta: American Cancer Society. [resource on the Internet]. 2010. Available from: <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-026238.pdf>.
- Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. *J Clin Oncol* 2010;28:3360–5.
- Borner C. The Bcl-2 protein family: sensors and checkpoints for life-or-death decisions. *Mol Immunol* 2003;39:615–47.
- Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014;32:3059–68.
- Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235–42.
- Coleman M, Martin P, Ruan J, et al. Prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) oral combination chemotherapy regimen for recurring/refractory lymphoma: low-dose metronomic, multidrug therapy. *Cancer* 2008;112:2228–32.
- Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. *Nat Rev Cancer* 2002;2:647–56.
- Cory S, Huang DC, Adams JM. The Bcl-2 family: roles in cell survival and oncogenesis. *Oncogene* 2003;22:8590–607.
- Czuczman MS, Grillo-López AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. *J Clin Oncol* 1999;17:268–76.
- Davis RE, Brown KD, Siebenlist U, et al. Constitutive nuclear factor kappaB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. *J Exp Med* 2001;194:1861–74.

- Gascoyne RD, Adomat SA, Krajewski S, et al. Prognostic significance of Bcl-2 protein expression and Bcl-2 gene rearrangement in diffuse aggressive non-Hodgkin's lymphoma. *Blood* 1997;90:244–51.
- Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010;28:4184–90.
- Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol* 2012;30:3460–7.
- Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of German Low-Grade Lymphoma Study Group. *Blood* 2005;106:3725–32.
- Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood* 2013;121:4021–31.
- International Agency for Research on Cancer, GLOBOCAN (IARC). Section of cancer information. [resource on the Internet]. 2008 [cited 2010 Nov 8]. Available from: <http://globocan.iarc.fr/factsheets/populations/factsheet.asp?unp=990>.
- Iqbal J, Meyer PN, Smith LM, et al. BCL2 predicts survival in germinal center B-cell-like diffuse large B-cell lymphoma treated with CHOP-like therapy and rituximab. *Clin Cancer Res* 2011;17:7785–95.
- Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol* 2012;30:3452–9.
- Lee JJ, Lui DD. A predictive probability design for phase II cancer clinical trials. *Clin Trials* 2008;5:93–106.
- Marsden VS, Strasser A. *Control of apoptosis in the immune system: B1-2, BH3-only proteins and more. Annu Rev Immunol* 2003;21:71–80.
- Mérino D, Khaw SL, Glaser SP, et al. Bcl-2, Bcl-x(L), and Bcl-w are not equivalent targets of ABT-737 and navitoclax (ABT-263) in lymphoid and leukemic cells. *Blood* 2012;119:5807–16.

- Morschhauser FA, Cartron G, Thieblemont C, et al. Obinutuzumab (GA101) in patients with relapsed/refractory diffuse large B-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN study. *J Clin Oncol* 2013;31:2912–9.
- Mossner E, Brunker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood* 2010;115:4393–402.
- National Comprehensive Cancer Network, Inc. NCCN Clinical Practice Guidelines in Oncology. [resource on the Internet]. 2010. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.
- Oldereid NB, Angelis PD, Wiger R, et al. Expression of Bcl-2 proteins and spontaneous apoptosis in normal human testis. Mol Hum Reprod* 2001;7:403–8.
- Persky DO, Dornan D, Goldman BH, et al. Fc gamma receptor 3a genotype predicts overall survival in follicular lymphoma patients treated on SWOG trials with combined monoclonal antibody plus chemotherapy but not chemotherapy alone. *Haematologica* 2012;97:937–42.
- Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20 B-cell lymphomas: a randomized controlled trial (RICOVER-60). *Lancet Oncol* 2008;9:105–16.
- Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). *Blood* 2013;122:1137–43.
- Robertson MJ, Kahl BS, Vose JM, et al. Phase II study of enzastaurin, a protein kinase C beta inhibitor, in patients with relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol* 2007;25:1741–6.
- Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:1937–47.
- Salles GA, Morschhauser F, Solal-Céligny P, et al. Obinutuzumab (GA101) in patients with relapsed/refractory indolent non-Hodgkin lymphoma: results from the phase II GAUGUIN study. *J Clin Oncol* 2013;31:2920–6.
- Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. *Blood* 2009;114:3533–7.
- Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 2007;109:1857–61.
- Souers AJ, Levenson JD, Boghaert ER, et al. ABT-199, a potent selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med* 2013;19:202–8.

- Sugiyama N, Obinata M, Matsui Y. Bcl-2 inhibits apoptosis of spermatogonia and growth of spermatogonial stem cells in a cell-intrinsic manner. Mol Reprod Dev 2001;58:30–8.*
- Valera A, Lopez-Guillermo A, Cardesa-Salzmann T, et al. MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. *Haematologica* 2013;98:1554–62.
- Visco C, Tzankov A, Xu-Monette ZY, et al. Patients with diffuse large B-cell lymphoma of germinal center origin with BCL2 translocations have poor outcome, irrespective of MYC status: a report from an International DLBCL rituximab-CHOP Consortium Program Study. *Haematologica* 2013;98:255–63.
- Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 2008;26:4952–7.
- Yamamura K, Kamada S, Ito S, et al. Accelerated disappearance of melanocytes in bcl-2-deficient mice. Cancer Res 1996;56:3546–50.*
- Yan W, Huang JX, Lax AS, et al. Overexpression of Bcl-W in the testis disrupts spermatogenesis: revelation of a role of BCL-W in male germ cell cycle control. *Mol Endocrinol* 2003;17:1868–79.
- Yeo W, Chan TC, Leung NW, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *J Clin Oncol* 2009;27:60511.

Appendix 1 Schedule of Assessments

Study Period	Screening Period	Treatment Period														Follow-Up Period			Participation End	
		DLT Observation Period (Cycle 1-Cycle 2) ^a						Cycle 3	Cycle 4	Cycles 5-6	Cycles 7-8	End of Treatment	Follow-Up	Survival Follow-up	End of Study/Early Study Termination					
		Cycle 1			Cycle 2															
Day of Cycle	Screening Once (-21 to -1)	1	4	5	8 (±1)	15 (±1)	1 (±2)	10	1 (±2)	10 (±2)	1 (±2)	10 (±2)	once (15-21)	1 (±2)	10 (±2)	1 (±2)	Cycle 8 Day 1 (or last cycle received) + 6-8 weeks	Every 3 months from End of Treatment visit (±14)	Every 6 months (±14)	
Informed consent	x																			
Demographic data	x																			
General medical history & baseline conditions	x																			
Concomitant medications & adverse events	x	x	x		x	x	x		x		x			x		x		x ^b		x ^b
ECOG Performance Status	x																x		x	
Complete physical examination	x																			
Targeted physical examination							x		x		x			x		x		x		x
Vital signs ^c	x	x	x ^d	x ^d	x	x	x		x		x			x		x		x		x
12-Lead ECG (in triplicate)	x																			
MUGA/Echocardiogram ^e	x																			
Clinical response assessment ^f							x		x		x			x		x		x		x
PET-CT scan & Response Assessment ^{g, h}	x ⁱ												x				x		x ^j	(x) ^k
Drug administration																				
Venetoclax (GDC-0199) ^l																				x (Cycle 1 Days 4-10, and Cycles 2-8 Days 1-10)

Appendix 1 Schedule of Assessments (cont.)

Study Period	Screening Period	Treatment Period														Follow-Up Period			Participation End
		DLT Observation Period (Cycle 1-Cycle 2) ^a						Cycle 3	Cycle 4	Cycles 5-6	Cycles 7-8	End of Treatment	Follow-Up	Survival Follow-up	End of Study/Early Study Termination				
		Cycle 1			Cycle 2														
Cycles of Treatment Period	Screening Once (-21 to -1)	1	4	5	8 (±1)	15 (±1)	1 (±2)	10	1 (±2)	10 (±2)	1 (±2)	10 (±2)	once (15-21)	1 (±2)	10 (±2)	1 (±2)	Cycle 8 Day 1 (or last cycle received) + 6-8 weeks	Every 3 months from End of Treatment visit (±14)	Every 6 months (±14)
Day of Cycle																			
Rituximab ^m		x					x		x		x			x		x			
Obinutuzumab ⁿ		x			x	x	x		x		x			x		x			
Cyclophosphamide ^o		x					x		x		x			x					
Doxorubicin ^o		x					x		x		x			x					
Vincristine ^o		x					x		x		x			x					
Prednisone ^{o,p}		x (daily)					x ^p		x ^p		x ^p			x					
Local laboratory assessments																			
Hematology ^q	x	x ^d	x ^d	x ^d	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Serum chemistries ^r	x	x ^d	x ^d	x ^d	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Serum pregnancy test ^s	x																		
HBV and HCV screening ^t	x																		
Hepatitis B DNA on PCR (as indicated) ^t	x						x		x		x			x		x	x	x	
Bone marrow biopsy/aspirate ^u	x ⁱ																(x) ^u	(x) ^u	(x) ^u
Central laboratory assessments																			
Blood sample for DLBCL NHL biomarker studies		x ^v																	

Appendix 1 Schedule of Assessments (cont.)

Study Period	Screening Period	Treatment Period														Follow-Up Period			Participation End	
Cycles of Treatment Period	Screening Once (-21 to -1)	DLT Observation Period (Cycle 1-Cycle 2) ^a						Cycle 3	Cycle 4	Cycles 5-6	Cycles 7-8	End of Treatment	Follow-Up	Survival Follow-up	End of Study/Early Study Termination					
		Cycle 1			Cycle 2															
Day of Cycle		1	4	5	8 (±1)	15 (±1)	1 (±2)	10	1 (±2)	10 (±2)	1 (±2)	10 (±2)	once (15-21)	1 (±2)	10 (±2)	1 (±2)	Cycle 8 Day 1 (or last cycle received) + 6-8 weeks	Every 3 months from End of Treatment visit (±14)	Every 6 months (±14)	
Tumor biopsy for <i>BCL2</i> family expression by IHC	x ^{i,w}																x ^x	x ^x		
Tissue punch for TMAs (in Phase II only)	x ^w																			
PK sample for venetoclax (GDC-0199)		See Appendix 3																		
PK sample for rituximab ^m		See Appendix 3																		
PK sample for obinutuzumab ⁿ		See Appendix 3																		
PK for CHOP components		See Appendix 3																		
Plasma sample for resistance markers ^y	x												x							x
Blood sample for lymphocyte subsets	x																	x	x ^z	
Blood sample for assessment of minimal residual disease MRD in Phase II only		x ^v										x						x	x ^{aa}	
Optional Roche Clinical Repository Sample(s) ^{bb}		(x) v																		
Contacts for Survival Follow-up ^{cc}																				x

BSA=body surface area; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisone; CR=complete response; CT=computed tomography; DLBCL=diffuse large B-cell lymphoma; DLT=dose-limiting toxicity; ECOG=Eastern Cooperative Oncology Group; G-CHOP=obinutuzumab+CHOP; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Hep C Ab=hepatitis C core antibody; IHC=immunohistochemistry; MRD=minimal residual disease; MUGA=Multiple-gated acquisition scan; NHL=non-Hodgkin's lymphoma;

Appendix 1

Schedule of Assessments (cont.)

PCR=polymerase chain reaction; PET=positron emission tomography; PK=pharmacokinetic; R-CHOP=rituximab+CHOP; RCR=Roche Clinical Repository; TMA=tissue microarray; (x)=indicates that time point may not apply to all patients, depending on specific requirements or patient consent.

- ^a If venetoclax dosing starts at Cycle 1 Day 1 or 2 then the DLT observation period would be shortened to one cycle.
- ^b All adverse events and medications to be reported for 30 days after the last dose of venetoclax or CHOP, or 90 days after the last dose of rituximab or obinutuzumab, whichever is later. After this period, serious adverse events or adverse events of special interest that are believed to be related to study drug treatment need to be reported.
- ^c Vital signs to include body temperature, heart rate, blood pressure, and weight. Height and BSA are only required at screening. Subsequent BSA required if > 10% change in weight.
- ^d Follow the specific time points described in Section [4.5.1.5](#).
- ^e Assessment of cardiac function is to be performed at screening (Day -21 to Day -1) and then as clinically indicated.
- ^f Clinical response assessment is to include physical examination for the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Does not include assessment based on imaging.
- ^g Imaging should be PET-CT at screening and 6–8 weeks after Cycle 8, Day 1 (or last cycle received). All others may be CT only.
- ^h Response assessment will be determined by the investigator on the basis of PET+CT and clinical assessment using *the modified Lugano Classification* (see [Appendix 2](#)). Response assessment should be determined on the basis of the imaging conducted on this day but is not required to be done on the same day.
- ⁱ All screening assessments to be conducted within 21 days prior to first dose with the exception of the PET-CT scan, tumor biopsy, and bone marrow biopsy/aspirate. See Section [4.5.2](#).
- ^j Required every 6 months for 2 years.
- ^k Assessment does not need to be performed if it has been performed within the last 30 days.
- ^l Venetoclax dosing on Cycle 1 Day 4 (or 3 days after first CHOP dose) to Cycle 1 Day 10 and then Cycles 2–8 Days 1–10. Alternative dosing regimens are possible based on data from initial cohorts per Protocol Section [3.1.2.2](#).
- ^m Arm A (R-CHOP) patients only.
- ⁿ Arm B (G-CHOP) patients only.
- ^o Patients who experience ongoing response without excessive toxicity may receive up to eight cycles of CHOP following discussion between the investigator and the Medical Monitor.
- ^p Prednisone days 1–5 of each Cycle 1–6.
- ^q Hematology to include complete blood count with platelets and WBC count differential.
- ^r Serum chemistries listed in Section [4.5.1.5](#).

Appendix 1 Schedule of Assessments (cont.)

- ^s Required for all women of reproductive potential (see inclusion criteria).
- ^t HBsAg, anti-HBcAb, and Hep C Ab serology (also HCV and RNA by polymerase chain reaction if the patient is HCV antibody positive) required. For hepatitis B core antibody–positive patients, the HBV-DNA titer should be determined using real-time PCR at baseline and monthly until at least 12 months after the last treatment cycle.
- ^u To be performed within 3 months prior to initiating therapy. If positive, *not done or indeterminate* at screening, should be repeated at end of therapy to document complete remission, if appropriate. Should be conducted at end of study and/or early termination only if CR was not previously confirmed at end of treatment.
- ^v This baseline sample may be collected at any time before starting treatment.
- ^w Sample must include 20 unstained, serial slides or a tissue block. In addition, if slides are sent a tissue punch from excisional biopsies must be taken from the tissue block for construction of TMAs in Phase II only. Tissue samples to be sent to the central laboratory within 3 weeks of patient randomization.
- ^x Only required at disease progression.
- ^y Plasma sample will be collected for analysis of circulating tumor markers of response/resistance at baseline (pre-dose), between Cycle 4 Day 15 and Cycle 5 Day 1, and at end of study and/or early termination visit.
- ^z Required only at months 6 and 12, and every 6 months thereafter until end of study.
- ^{aa} Required every 3 months for 1 year.
- ^{bb} Optional blood sample is requested at baseline for collection and storage at the RCR. Any samples at the central laboratories except the PK samples that remain from the planned study assessments may be taken and sent to the RCR if the patient consents to the optional RCR sampling.
- ^{cc} *Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 6 months until death, loss to follow-up, consent withdrawal, or study termination by Roche, whichever occurs first.*

Appendix 2

The Modified Lugano Classification: Revised Criteria for Response Assessment

Responses should be determined on the basis of radiographic and clinical evidence of disease. Assessment of positron emission tomography (PET)-computed tomography (CT) should follow the Recommendations for Initial Evaluation, Staging, and Response Assessment for Hodgkin and Non-Hodgkin's Lymphoma: The Lugano Classification described by [Cheson \(2014\)](#), is presented in the Revised Criteria for Response Assessment table with the following modifications: (1) For complete response (CR), if the bone marrow was involved by lymphoma *or indeterminate* prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy; (2) For PET-CT-based partial response (PR), CT criteria for PR (or CR) must also be met.

Selection of measured dominant (indicator) lesions:

- Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters
 - A measurable node must have a longest transverse diameter of a lesion (LDi) > 1.5 cm.
 - A measurable extranodal lesion should have an LDi > 1.0 cm.
- Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.
- Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, and lungs), gastrointestinal (GI) involvement, cutaneous lesions, or those noted on palpation.
- If possible, they should be from disparate regions of the body
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

Selection of non-measured (non-indicator) lesions:

- Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured.
 - These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, and bone marrow), ¹⁸F-fluorodeoxyglucose (FDG) uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal

Appendix 2

The Modified Lugano Classification: Revised Criteria for Response Assessment (cont.)

physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

Appendix 2

The Modified Lugano Classification: Revised Criteria for Response Assessment (cont.)

Response	Site	PET-CT–Based Response	CT-Based Response
Complete		Complete metabolic response	Complete radiologic response (all of the following)
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3 ^a with or without a residual mass on 5PS ^b It is recognized that in Waldeyer’s ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi. No extralymphatic sites of disease.
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy.	If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy.
Partial		Partial metabolic response	Partial remission (all of the following)
	Lymph nodes and extralymphatic sites	Score of 4 or 5 ^b with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease. CT-based response criteria for PR (or CR) must also be met.	≥ 50% decrease in SPD of up to 6 target measureable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. When no longer visible, 0 × 0 mm. For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation.
	Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase.

Appendix 2

The Modified Lugano Classification: Revised Criteria for Response Assessment (cont.)

Response	Site	PET-CT–Based Response	CT-Based Response
	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 for up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
	Nonmeasured 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
Progressive Disease		Progressive metabolic disease	Progressive disease (requires at least 1 of the following)
	Individual target nodes/nodal lesions	Score 4 or 5 ^b with an increase in intensity of uptake from baseline.	PPD progression: An individual node/lesion must be abnormal with: <ul style="list-style-type: none"> • 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
		<i>and/or</i>	

Appendix 2

The Modified Lugano Classification: Revised Criteria for Response Assessment (cont.)

Response	Site	PET-CT–Based Response	CT-Based Response
Extranodal lesions		New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment.	
Nonmeasured lesion		None	New or clear progression of preexisting
Organ enlargement			In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline.
		<i>and/or</i>	New or recurrent splenomegaly.
New lesions		New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions. A new node > 1.5 cm in any axis. A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma.
		<i>and/or</i>	Assessable disease of any size unequivocally attributable to lymphoma.
Bone marrow		New or recurrent FDG-avid foci.	New or recurrent involvement

5-PS=5-point scale; CR=complete response; CT=computed tomography; FDG=fluorodeoxyglucose; GI=gastrointestinal; LDi=longest transverse diameter of a lesion; MRI=magnetic resonance imaging; PET=positron emission tomography; PPD=cross product of the LDi and perpendicular diameter; PR=partial response; 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 scored at the time of an interim scan. However, in studies involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

^b PET 5-PS: 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 Pharmacokinetic Samples

Table 1 Pharmacokinetic *Blood* Sampling for Venetoclax+R-CHOP (ARM A) in Phase I

Visit	Time ^a	Event
Cycle 1 Day 1	Pre-dose	PK–rituximab PK–C, H, O, P
	End of rituximab infusion	PK–rituximab
	End of C,H, O administration	PK–C, H, O
	30 minutes after end of P administration	PK–P
	1 hour after end of P administration	PK–P
	2 hours after end of P administration	PK–P
	4 hours after end of P administration	PK–P
	6 hours after end of P administration	PK–P
Cycle 1 Day 4 (or first day of venetoclax dosing)	Pre-dose	PK–venetoclax
	2 hours after venetoclax dose	PK–venetoclax
	4 hours after venetoclax dose	PK–venetoclax
	6 hours after venetoclax dose	PK–venetoclax
	8 hours after venetoclax dose	PK–venetoclax
Cycle 1 Day 8	Pre-dose	PK–venetoclax
	8 hours after venetoclax dose	PK–venetoclax
Cycle 2 Day 1	Pre-dose	PK–rituximab PK–C, H, O, P
	End of C, H, O administration	PK–C, H, O
	30 minutes after end of P administration	PK–P
	1 hour after end of P administration	PK–P
	2 hours after end of P administration	PK–P
	4 hours after end of P administration	PK–P
	6 hours after end of P administration	PK–P
Cycle 2 Day 10	Pre-dose	PK–venetoclax
Cycles 3–8 Day 1	Pre-dose	PK–rituximab
End of treatment (Cycle 8 Day 1+6–9 weeks)	Any time during visit	PK–rituximab

C = cyclophosphamide; H = doxorubicin; O = vincristine; P = prednisone; PK = pharmacokinetic.

^a Pre-dose samples must be taken within 30 minutes prior to the administration of dose; all other samples must be taken within a ± 15 minute window from the scheduled time.

Appendix 3 Pharmacokinetic Samples (cont.)

Table 2 Pharmacokinetic *Blood* Sampling for Venetoclax+G-CHOP (Arm B) in Phase I

Visit	Time ^a	Event
Cycle 1 Day 1	Pre-dose	PK–obinutuzumab PK–C, H, O, P
	End of obinutuzumab infusion	PK–obinutuzumab
	End of C,H, O administration	PK–C, H, O
	30 minutes after end of P administration	PK–P
	1 hour after end of P administration	PK–P
	2 hours after end of P administration	PK–P
	4 hours after end of P administration	PK–P
	6 hours after end of P administration	PK–P
Cycle 1 Day 4 (or first day of venetoclax dosing)	Pre-dose	PK–venetoclax
	2 hours after venetoclax dose	PK–venetoclax
	4 hours after venetoclax dose	PK–venetoclax
	6 hours after venetoclax dose	PK–venetoclax
	8 hours after venetoclax dose	PK–venetoclax
Cycle 1 Day 8	Pre-dose	PK–venetoclax
	8 hours after venetoclax dose	PK–venetoclax
Cycle 2 Day 1	Pre-dose	PK–obinutuzumab PK–C, H, O, P
	End of C, H, O administration	PK–C, H, O
	30 minutes after end of P administration	PK–P
	1 hour after end of P administration	PK–P
	2 hours after end of P administration	PK–P
	4 hours after end of P administration	PK–P
	6 hours after end of P administration	PK–P
Cycle 2 Day 10	Pre-dose	PK–venetoclax
Cycles 3–8 Day 1	Pre-dose	PK–obinutuzumab
End of treatment (Cycle 8 Day 1+6–9 weeks)	Any time during visit	PK–obinutuzumab

C = cyclophosphamide; H = doxorubicin; O = vincristine; P = prednisone; PK = pharmacokinetic.

^a Pre-dose samples must be taken within 30 minutes prior to the administration of dose; all other samples must be taken within a ± 15 minute window from the scheduled time.

Appendix 3 Pharmacokinetic Samples (cont.)

Table 3 Pharmacokinetic *Blood* Sampling in Phase II for Approximately the First 20 Patients in Arm A

Visit	Time ^a	Event
Cycle 1 Day 4 (or first day of venetoclax dosing)	Pre-dose	PK–venetoclax
	2 hours after venetoclax dose	PK–venetoclax
	4 hours after venetoclax dose	PK–venetoclax
	6 hours after venetoclax dose	PK–venetoclax
Cycle 1 Day 8	8 hours after venetoclax dose ^b	PK–venetoclax
	Pre-dose	PK–venetoclax
Cycle 1 Day 8	8 hours after venetoclax dose ^b	PK–venetoclax
	Pre-dose	PK–venetoclax
Cycle 2 Day 10	Pre-dose	PK-venetoclax

PK = pharmacokinetic.

^a Pre-dose samples must be taken within 30 minutes prior to the administration of dose; all other samples must be taken within a ± 15 minute window from the scheduled time.

^b These samples are not optional, however, due to the complexity of the sample collection and processing the Sponsor recognizes that some centers may not have the capability to collect these PK samples. In those instances, these PK samples will not be collected. These samples can be taken within a -1 hr/+20 min window.

Table 4 Pharmacokinetic *Blood* Sampling in Remaining Phase II Patients

Visit	Time ^a	Event
Cycle 1 Day 8	Pre-dose	PK–venetoclax
Cycle 2 Day 10 ^b	Pre-dose	PK-venetoclax
	4–6 hours after venetoclax dose	PK-venetoclax
Cycle 3 Day 10 ^c	Pre-dose	PK-venetoclax
Cycle 4 Day 10 ^c	Pre-dose	PK-venetoclax

^a Pre-dose samples must be taken within 30 minutes prior to the administration of dose; all other samples must be taken within a ± 15 minute window from the scheduled time.

^b Note that there is no window for this visit. It must occur on Day 10.

^c Note that the window for the participating sites must be adjusted to -2 + 1 day (rather than ± 2 days) for this visit.

Appendix 4 Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Appropriate monitors (ECG, blood pressure, pulse oximetry)
- Oxygen
- Epinephrine for intravenous (IV), intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional assistance!
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continual ECG and pulse oximetry monitoring, if possible.
- Administer 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 5

Sample List of Excluded and Cautionary Medications

	Type of Inducer, Inhibitor or Substrate	Medication Name
Excluded medications during Ramp-Up and throughout the DLT assessment period (if applicable) and cautionary at the final dose of venetoclax, once the DLT assessment period is complete	Strong CYP3A inducers	Avasimibe, carbamazepine (Tegretol [®]), phenobarbital, phenytoin (Dilantin [®]), rifampin (Rifadin [®]), St. John's wort.
	Moderate CYP3A inducers	Bosentan, efavirenz, etravirine, modafinil, nafcillin.
	Strong CYP3A inhibitors	Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole.
	Moderate CYP3A inhibitors	Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib ^a , darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib ^a , verapamil.
Cautionary medications throughout the study		Warfarin
	Weak CYP3A inducers	Amprenavir, aprepitant, armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, vemurafenib ^a .
	Weak CYP3A inhibitors	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide ^a , cilostazol, cimetidine, cyclosporine ^a , fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib ^a , oral contraceptives, pazopanib ^a , ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, zileuton.
	P-gp substrates	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus ^a , fexofenadine, lapatinib ^a , loperamide, maraviroc, nilotinib ^a , ranolazine, saxagliptin, sirolimus ^a , sitagliptin, talinolol, tolvaptan, topotecan ^a .
	BCRP substrates	Methotrexate ^a , mitoxantrone ^a , irrinotecan ^a , lapatinib ^a , rosuvastatin, sulfasalazine, topotecan ^a .
	OATP1B1/1B3 substrates	Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan.
	P-gp inhibitors	Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, ronalzine, ticagrelor.
	BCRP inhibitors	Gefitinib ^a , cyclosporine ^a .
	OATP1B1/B3 inhibitors	Gemfibrozil, eltrombopag, cyclosporine ^a , tipranavir.

DLT = dose-limiting toxicity; P-gp = P-glycoprotein.

Note(s): This is not an exhaustive list. For an updated list, see the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm> In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruits.

^a These are anti-cancer agents; contact the Genentech Medical Monitor before use. After discontinuation of the strong or moderate CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.

Appendix 6

Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax

First dose of venetoclax or dose increase:

- Within the first 24 hours after either the first dose or dose increase, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted and/or contacted on admission (per institutional standards to ensure emergency dialysis is available).
- Intravenous (IV) fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not <50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (TLS; e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be as per institutional protocols.

Appendix 6

Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax (cont.)

Abnormality	Findings	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium WNL)	<ul style="list-style-type: none"> Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. If further ≥ 0.2 mmol/L increase in potassium, but still $< \text{ULN}$, manage as per potassium $\geq \text{ULN}$. Otherwise recheck in 1 hour. Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium $< \text{ULN}$, and no other evidence of tumor lysis. At discretion of investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
	Potassium $> \text{ULN}$	<ul style="list-style-type: none"> Perform immediate ECG and commence telemetry. Nephrology notification with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg IV $\times 1$. Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. If potassium $< \text{ULN}$ 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
	Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	<ul style="list-style-type: none"> Perform immediate ECG and commence telemetry. Nephrology assessment with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg IV $\times 1$. Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. Administer sodium bicarbonate 1 to 2 mEq IV push. If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour.
Hyperuricemia	Uric acid ≥ 8.0 mg/dL (476 $\mu\text{mol/L}$)	<ul style="list-style-type: none"> Consider rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour.

Appendix 6

Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax (cont.)

Abnormality	Findings	Management Recommendations
Hypocalcemia	Uric acid ≥ 10 mg/dL (595 μmol/L) <u>OR</u> Uric acid ≥ 8.0 mg/dL (476 μmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	<ul style="list-style-type: none"> • Administer rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
	Calcium ≤ 7.0 mg/dL (1.75 mmol/L) <u>AND</u> Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	<ul style="list-style-type: none"> • Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	<ul style="list-style-type: none"> • Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	Increase ≥ 25% from baseline	<ul style="list-style-type: none"> • Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours.

IV = intravenous; ULN = upper limit of normal; WNL = within normal limits.

Appendix 6

Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax (cont.)

Ongoing dosing of venetoclax:

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose increase (e.g., 48 or 72 hours) are as stated below. Note: If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.

Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (see table above).

- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus, and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (see table above).

Appendix 7

International Prognostic Index and Ann Arbor Staging Classification

International Prognostic Index

The International Prognostic Index for aggressive non-Hodgkin's lymphoma identifies five significant risk factors that are prognostic of overall survival (OS):

Risk Factors	
<i>Ann-Arbor Stage III or IV</i>	
<i>Age >60 years</i>	
<i>Elevated LDH</i>	
<i>ECOG performance status ≥ 2</i>	
<i>Extranodal involvement ≥ 2</i>	
<i>IPI Risk Group</i>	<i>Number of IPI Risk Factors</i>
<i>Low</i>	<i>0 or 1</i>
<i>Low-intermediate</i>	<i>2</i>
<i>High-intermediate</i>	<i>3</i>
<i>High</i>	<i>4 or 5</i>

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index.

Ann Arbor Staging Classification for Hodgkin and Non-Hodgkin's Lymphoma

<i>Stage I</i>	<i>Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE) ^a</i>
<i>Stage II</i>	<i>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)</i>
<i>Stage III</i>	<i>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)</i>
<i>Stage IV</i>	<i>Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement</i>

^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.

All cases are subclassified to indicate the absence (A) or presence (B) of the **systemic ("B") symptoms** of significant unexplained fever ($>38^{\circ}\text{C}$), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

Appendix 7

International Prognostic Index and Ann Arbor Staging Classification (cont.)

Clinical stage refers to the extent of disease determined by diagnostic tests following a single diagnostic biopsy. If a second biopsy of any kind is obtained, even if negative, the term pathologic stage is used.

Adapted from:

1. *Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971;31:1860-1.*
2. *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.*