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**
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STATISTICAL ANALYSIS PLAN

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

STUDY DRUGS: Venetoclax (GDC-0199; ABT-199; RO5537382)
Obinutuzumab (GA101; RO5072759)

VERSION NUMBER: 1

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PLAN PREPARED BY: [redacted]

DATE FINAL: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	24-Jan-2017 00:08:33

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
ABC	activated B cell
AUC	area under the concentration–time curve
BOR	best overall response
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
CL/F	apparent clearance
CT	computed tomography
DE	double expressor
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DR	double robust
ECOG	Eastern Cooperative Oncology Group
FISH	fluorescence in situ hybridization
G	obinutuzumab (GA101)
GCB	germinal center B cell
IHC	immunohistochemistry
IMC	Internal Monitoring Committee
IPI	International Prognostic Index
IRC	Independent Review Committee
IRR	infusion-related reaction
ITT	intent-to-treat
MRD	minimal residual disease
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
OS	overall survival
OR	objective response
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival

Abbreviation or Term	Definition
PK	pharmacokinetic
PR	partial response
QD	once daily
R	rituximab
SOC	Scientific Oversight Committee
$T_{1/2}$	Half-life
TLS	tumor lysis syndrome
t_{max}	time to maximum observed plasma concentration
V	volume of distribution

1. BACKGROUND

Study GO27878 was developed to explore the safety of venetoclax (VENCLEXTA™, also known as GDC-0199; ABT-199) in combination with rituximab (R) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy (venetoclax + R-CHOP) or venetoclax in combination with obinutuzumab (G) plus CHOP (venetoclax + G-CHOP) in patients with B-cell non–Hodgkin's lymphoma (NHL) who are believed to be appropriate candidates for R-CHOP therapy during initial dose-finding cohorts, and to further explore safety and efficacy in Phase II in patients with previously untreated diffuse large B-cell lymphoma (DLBCL) in order to identify appropriate populations for evaluation in a Phase III setting.

This document is based on the statistical section of the study protocol and provides details regarding the planned statistical analyses of the safety and efficacy of venetoclax + R-CHOP and venetoclax + G-CHOP in patients with previously untreated DLBCL who are enrolled in the Phase II portion of the study. Key analyses will focus on a subset of patients (i.e., patients with double expressor [DE] DLBCL), characterized by high expression of both BCL-2 and c-MYC proteins, and has a poor prognosis to R-CHOP treatment (Green et al. 2012; Johnson et al. 2012; Hu et al. 2013; Valera et al. 2013). This analysis may support potential registration for venetoclax + R-CHOP in patients with DE DLBCL. Any analyses that are beyond those outlined in the protocol are delineated in this document.

2. STUDY DESIGN

This is a Phase Ib/II, multicenter, open-label, dose-finding study of venetoclax administered orally in combination with rituximab or obinutuzumab plus standard doses of CHOP in patients with NHL. Two parallel treatment arms explored doses of venetoclax that had a range of 200–800 mg once daily (QD) administered in combination with R-CHOP or G-CHOP (see Figure 1). Patients were treated for a total of eight 21-day cycles (8 cycles of venetoclax + rituximab or venetoclax + obinutuzumab plus CHOP for the first 6 cycles). Patients who experienced ongoing responses without excessive toxicity may receive up to 8 cycles of CHOP following discussion between the investigator and the Medical Monitor.

The study was designed with two stages: a Phase Ib dose-finding stage and a Phase II expansion stage. During the Phase Ib stage, the safety profile of venetoclax in combination with R-CHOP (Arm A) or with G-CHOP (Arm B) was to be determined separately for each arm. The corresponding determined venetoclax dose level for each arm was used in the Phase II stage for that arm, unless safety or tolerability signals suggested a lower dose more appropriate, or other evidence showed no need of further development.

No maximum tolerated dose (MTD) could be identified at any dose level tested for Arm A, and the safety profile of the combination treatment (up to venetoclax 800 mg) was

characterized as safe to go forward based on assessments of dose-limiting toxicities (DLTs) and overall tolerability.

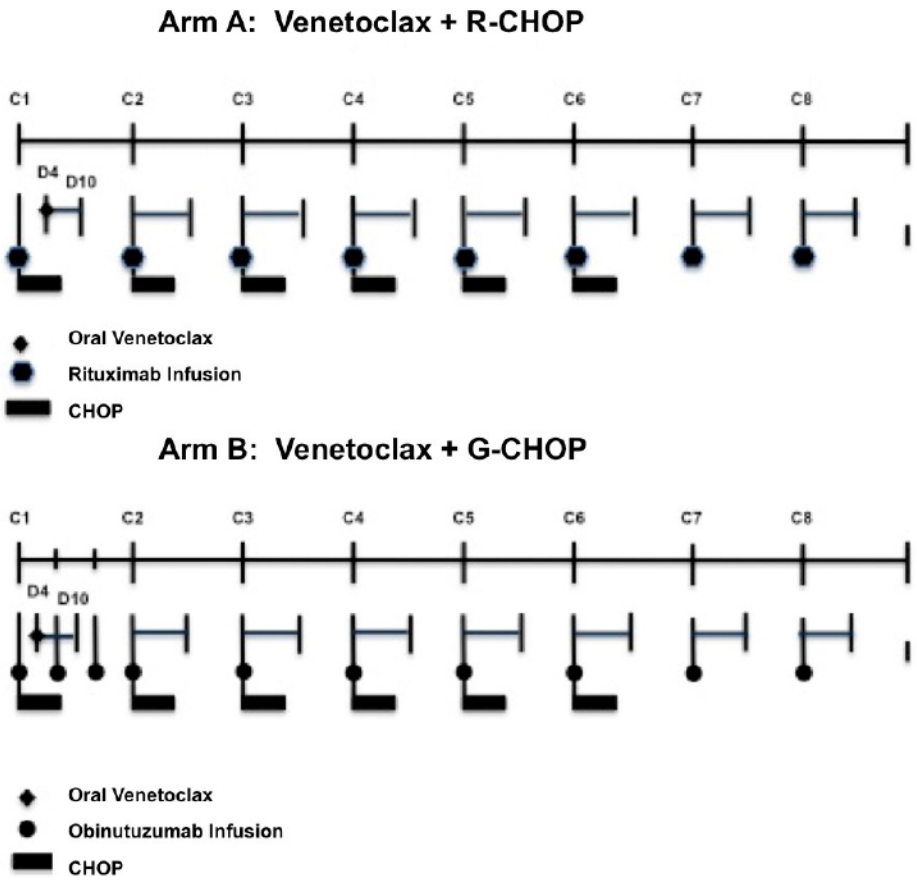
The study enrolled 32 patients during the dose-finding phase for venetoclax + G-CHOP arm, which contains 4 dose-finding cohorts exploring venetoclax doses and dosing schedule ranging from 200 to 800 mg. As the Study BO21005 that compared R-CHOP with G-CHOP for patients with front-line DLBCL did not meet the primary endpoint of progression-free survival (PFS), the Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC) decided not to open Phase II for Arm B for patients with DLBCL.

For the venetoclax + R-CHOP Phase II portion of the study, the venetoclax dose selected for venetoclax + R-CHOP arm was 800 mg QD on Days 4–10 of Cycle 1 and Days 1–10 of Cycles 2–8, as determined by the Phase Ib portion of the study (see Protocol Version 8, Section 3.2.3 for justification).

The study enrolled 211 patients in the Phase II portion for venetoclax + R-CHOP arm, in order to enroll at least approximately 50 patients with DE DLBCL and approximately 80–100 patients with high BCL-2 expression (approximately 40–50 patients each for germinal center B cell [GCB] and activated B cell [ABC] cell of origin subtypes) at up to 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 are performed following 4 cycles of study treatment (i.e., during Cycle 4, between Days 15 and 21) and at the completion of study treatment (6–8 weeks from Day 1 of Cycle 8 or last cycle received), and during follow up visits post end of treatment assessment until study is terminated.

Figure 1 Study Schema



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

If there were 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 may be explored based on the guideline provided in Protocol Version 8, Section 4.3.

After the first 20 patients in the venetoclax+R-CHOP arm of the Phase II portion of the study have completed Cycles 1 and 2 of study treatment, the IMC and SOC will meet to review safety data for all patients treated in both the Phase Ib and 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 be continued while the interim safety analysis is being conducted.

Based on this review, changes may be made to the dose or the dosing schedule of study treatment in Phase II (see Protocol Section 3.2.3).

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is included in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 3.

2.2 OUTCOME MEASURES

All measurable disease must be documented at screening by a combined positron emission tomography and computed tomography (PET-CT) scan and contrast CT, and re-assessed at each subsequent tumor evaluation by at least a CT scan except for end of treatment assessment (i.e., PET-CT is required for end of treatment assessments, whereas CT scan is acceptable for assessments during Cycle 4 and follow-up). Response assessments will be determined by the Independent Review Committee (IRC) and by the investigator on the basis of imaging studies and bone marrow biopsy sample results if applicable, with the use of the following:

- The modified Lugano Criteria (see Appendix 4; and Appendix 2 of the Study GO27878 Protocol), a modification based on Cheson et al. 2014

  Confirm PET complete response (CR) by cleared bone marrow involvement at end of treatment if bone marrow was involved by lymphoma or indeterminate prior to treatment.

  Confirm PET partial response (PR) by CT PR (or CR).
- Lugano Classification (Cheson et al. 2014)

A summary of response based efficacy endpoints is shown in Table 1.

Table 1 Summary of Response Endpoints

Response Endpoint	Definition	Primary	Secondary
PET/CT-CR (modified Lugano)	PET-CR or CT-CR (if PET scan is missing or not evaluable) rate, where CR is assessed according to modified Lugano 2014 per protocol Appendix 4 for PET and ordinary Lugano for CT. CR is downgraded to PR if there is a positive bone marrow biopsy tissue sample result at the time of CR assessment, or if the baseline bone marrow biopsy sample result is positive and missing at the time of the CR assessment.	IRC at end of treatment	Investigator at end of treatment
PET/CT-CR (Lugano)	PET-CR or CT-CR Lugano 2014 (if PET scan is missing or not evaluable) rate at end of treatment	—	Investigator at end of treatment
CT-CR	Lugano 2014 classification with use of CT imaging only	—	IRC and/or investigator at end of treatment
OR (PET/CT)	PET-CR or PR or CT-CR or PR (if PET scan is missing or not evaluable) rate at end of treatment	—	IRC and/or investigator at end of treatment
DOR (PET/CT-CR)	Time from the first documented occurrence of CR by PET or CT until PET or CT PD or death for the subgroup of patients achieving PET/CT-CR (modified Lugano) at end of treatment	—	IRC, investigator
DOR (BOR)	Time from the first documented occurrence of CR or PR by PET or CT until PET or CT PD or death for the subgroup of patients achieving best overall response of CR or PR by PET or CT	—	IRC, investigator

BOR=best overall response; CR=complete response; CT=computed tomography; DOR=duration of response; IRC=Independent Review Committee; OR=objective response; PD=progressive disease; PET=positron emission tomography; PR=partial response.

2.2.1 Primary Efficacy Outcome Measures

The primary efficacy outcome measures for Phase II portion is

- Complete response (PET/CT-CR [modified Lugano]) rate at end of treatment by IRC assessment using PET/CT, defined as the proportion of patients with either:

  PET-CR when PET is performed, according to the modified Lugano Classification: Revised Criteria for Response Assessment (see Appendix 4; Cheson et al. 2014) that incorporates PET assessments according to the Deauville criteria (Barrington et al. 2014). The modification downgrades CR to PR if there is a positive bone marrow biopsy sample result at time of the CR assessment or if the baseline bone marrow biopsy sample result is positive and missing at the time of the CR assessment

  or

  CT-CR when PET assessment is not performed or not evaluable, according to Lugano 2014 classification,

  at completion of venetoclax+R-CHOP treatment (6–8 weeks after Cycle 8 Day 1 for patients completing therapy or 6–8 weeks after Day 1 of last cycle visit for patients discontinuing treatment early). This will be assessed for:

- Previously untreated patients with DLBCL
- Previously untreated patients with DLBCL co-expressing BCL-2 and c-MYC protein (i.e., DE DLBCL) as defined through central laboratory testing with use of the Ventana immunohistochemistry (IHC) investigational-use-only assay and prespecified scoring algorithm (see Appendix 6) by both of the following criteria:

  BCL-2 high (2+, 3+)

  c-MYC positive: patient samples are considered MYC-positive if ≥40% of tumor cells demonstrate positive MYC nuclear staining (i.e. ≥40% of IHC positive nuclear stain [1+, 2+, or 3+])

2.2.2 Secondary Efficacy Outcome Measures

The following secondary efficacy outcome measures will be assessed for all patients with DLBCL and DE DLBCL:

- PET/CT-CR (modified Lugano) rate at end of treatment by investigator
- PET/CT-CR (Lugano) rate at end of treatment by investigator
- Overall survival (OS), defined as the time from date of enrollment 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.

The below secondary efficacy outcome measures will be assessed both by IRC assessment and by investigator assessment for all patients with DLBCL and DE DLBCL:

- CT-CR rate at end of treatment, as defined by CT scan only imaging assessed by Lugano 2014 classification (Cheson et al. 2014).

- Objective response (OR) rate (PET/CT), defined as PR or CR at end of treatment by PET according to the modified Lugano 2014 criteria when PET is available and by CT according to Lugano 2014 when PET is missing or not evaluable. All other cases are designated non-responders.
- Duration of response (DOR; PET/CT-CR), defined as the time from the first occurrence of a documented CR by PET or CT, to the date of disease progression by PET or CT, relapse, or death from any cause, for the subgroup of patients with end of treatment PET/CT-CR (modified Lugano). For patients achieving an end of treatment PET/CT-CR but who have not had disease progression, relapsed, or died at the time of analysis, DOR-PET/CT-CR will be censored on the date of last tumor assessment.
- Duration of overall response and best overall response (BOR), defined as the time from the first occurrence of a documented CR or PR by PET or CT, to the date of disease progression by PET or CT, relapse, or death from any cause, for the subgroup of patients with best overall response of CR or PR by PET or CT. For patients achieving a response but who have not had disease progression, relapsed, or died at the time of analysis, DOR will be censored on the date of last tumor assessment.
- PFS, defined as the time from date of enrollment to the first occurrence of progression as assessed by either PET or CT, or death from any cause. Patients who have not had disease progression, relapsed, nor died at the time of analysis will be censored on the date of last tumor assessment. If no tumor assessments were performed after the baseline visit, PFS will be censored at the date of enrollment.

2.2.3 Exploratory Efficacy Outcome Measures

The exploratory outcome measures of this study are the following:

- Minimal residual disease (MRD) negativity rate (% MRD negative) for patients who were MRD positive at baseline, at end of treatment and overall.
- Assessment of the key biomarkers that might predict disease response or resistance to treatment with venetoclax + R-CHOP, including:

  Patients who are either BCL-2 high or BCL-2 low as defined by central laboratory testing with use of the Ventana investigational-use-only IHC assay

  ABC and GCB cell-of-origin subtypes

  In patients who are either BCL-2 positive or BCL-2 negative within cell-of-origin subtypes

  In patients who have Double-Hit lymphoma, defined by the double translocation of BCL-2 and MYC by fluorescence in situ hybridization (FISH); and in patients who are non-Double Hit

  In patients with DE within cell-of-origin subtypes

  In DE patients within non-double hit patients (excluding double-hit)

  In patients with BCL-2 who are FISH positive or FISH negative

In patients with MYC who are FISH positive or FISH negative

In patients with BCL-2 with IHC sub-categories defined by the 4 clinical scores (0, 1+, 2+, 3+)

- Other biomarkers of potential interest include expression of BCL-2 family members; frequently mutated genes in DLBCL; cancer immunotherapy biomarkers

2.2.4 Pharmacokinetic Outcome Measures

The following pharmacokinetic (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 (area under concentration–time curve [AUC])
- Time to maximum observed plasma concentration (t_{max})
- Maximum observed plasma concentration (C_{max})
- Minimum plasma concentration under steady-state conditions within a dosing interval in (C_{min}) 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 apparent clearance (CL/F), volume of distribution (V), and half-life ($T_{1/2}$) may also be calculated as data allow.

2.2.5 Safety Outcome Measures

The safety and tolerability of venetoclax+R and G-CHOP will be assessed with use of the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events and serious adverse events graded according to the 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 to rituximab or obinutuzumab, and Grade ≥4 tumor lysis syndrome (by Howard criteria with Common Terminology Criteria grade determined by investigator). Selected adverse event analysis includes febrile neutropenia, thrombocytopenia, and infections.
- Changes in relevant clinical laboratory test results (including hematology and chemistry) and vital signs
- Maintenance of relative dose intensity of venetoclax+R-CHOP chemotherapy

2.3 DETERMINATION OF SAMPLE SIZE

The expected enrollment for the venetoclax+R-CHOP arm in Phase II is approximately 160–200 patients in order to enroll approximately 50 patients with DE DLBCL,

80–100 BCL-2 positive patients, and approximately 40–50 BCL-2 positive patients each in the GCB and the ABC subgroups. With 50 patients, 95% CIs for estimation of PET-CR would have a margin of error that would not exceed ±16%. The margin of error would decrease to 9% with 150 patients and to 8% with 200 patients. Table 2 shows Clopper and Pearson (1934) 95% CIs for expected observed rates for sample sizes of 50, 100, 150, and 200 patients.

Table 2 95% CIs for Expected Observed Rates for Sample Sizes

	Complete Response Rate (CI)			
Venetoclax+R-CHOP	50 Patients	100 Patients	150 Patients	200 Patients
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; CHOP=cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone; R=rituximab.

Table 3 gives the power of sample size with 50 patients in rejecting a null hypothesis of response rate equal to a specified value p_0:

Table 3 Power and Minimum Detectable Difference at Two-Sided 0.05 Level by Exact Test

	Power and MDD with two-sided alpha=0.05 (n=50 patients)			
Exact test	p=0.65		p=0.7	
Null hypothesis	Power (%)	MDD (%)	Power (%)	MDD (%)
$p_0=0.45$	81	0.60	95	0.60
$p_0=0.5$	51	0.66	78	0.66
$p_0=0.55$	28	0.70	57	0.70
$p_0=0.6$	7	0.76	22	0.76

MDD=minimum detectable difference.

There will be approximately 80% power if the true response is 20% better than as assumed in the null hypothesis. The observed response rate needs to be approximately 15% larger than control so that a statistically positive result could be obtained.

2.4 ANALYSIS TIMING

The primary analysis will occur after all patients enrolled and dosed in the venetoclax+R-CHOP arm complete the end-of-treatment response assessment or early discontinuation assessment. It is expected that this analysis will occur approximately 24 months after start of Phase II enrollment.

Additionally, interim analyses will be incorporated into the Phase II portion of venetoclax + R-CHOP arm in order to plan for future development. There are three planned interim analyses for safety and efficacy. A safety interim analysis specified per protocol will be performed after 20 patients are enrolled in venetoclax + R-CHOP arm of Phase II and have completed 2 cycles of combination therapy. During this analysis, data will be reviewed by IMC + SOC in order to assess safety and tolerability of the combination in a larger number of patients. Refer to Section 3.3 for more details on IMC and SOC review scope. The first and second efficacy interim analyses will be performed after approximately 40 and 70 patients complete end of treatment response assessments, respectively, in the venetoclax + R-CHOP arm of the Phase II portion. Safety information will be obtained at all interim analyses. Additional interim analyses may be conducted to guide future development before or after primary analysis.

R-CHOP data from completed Study BO21005 (GOYA, see Appendix 2) will be used as historical control for venetoclax + R-CHOP. Historical PET/CT-CR rates in patients with DE DLBCL and in intent-to-treat (ITT) patients whose samples are considered to be within stability window are expected to be available from GOYA Study for comparison by the time of first interim efficacy analysis.

3. STUDY CONDUCT

3.1 METHOD OF TREATMENT ASSIGNMENT

In the Phase Ib portion of this study, patients will be assigned to dose levels in the order in which they are enrolled. This is an open-label study. 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 International Prognostic Index (IPI) score of 2–5 will be enrolled.

3.2 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 sample results, and relevant clinical data, and will be guided by a charter specific to the independent review.

For all investigator-assessed response analyses, including PFS, there will be a corresponding analysis of the IRC-determined data.

3.3 DATA MONITORING

An IMC and an SOC has been established to monitor patient safety and to provide a recommendation for each treatment arm on the dose to be taken forward into the

Phase II portion of the study after completion of the dose-escalation phase. The IMC includes the Genentech Medical Monitor and at least 1 other medical doctor or clinical science representative not directly involved in the study, as well as representatives from drug safety, biostatistics, and statistical programming and analysis. The SOC is comprised of experts in DLBCL who are investigators for this study in order to provide guidance and a review of safety-related events. Separate IMC and SOC agreements outline each committee's composition, meeting timelines, and members' roles and responsibilities. The committee members review all potential cases of serious adverse events, Grade 3 and 4 adverse events, and deaths as specified in the IMC and SOC agreement. The SOC is kept apprised of all relevant efficacy and safety data from this study and other related clinical studies. Ad hoc meetings may be called in addition to scheduled quarterly meetings as necessary to provide recommendations on management of any new safety issues.

4. STATISTICAL METHODS

The analyses outlined in this section are for the Clinical Study Report preparation of venetoclax + R-CHOP arm at end of Phase II of the study.

Except where otherwise specified, all continuous variables will be summarized with use of descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum, and maximum) and all categorical variables will be summarized with use of frequency counts and percentages. Phase Ib results will be presented by venetoclax treatment group (venetoclax + G-CHOP or venetoclax + R-CHOP) and dose cohort. Phase II results will be presented separately and as a pooled 800 mg venetoclax treatment group by pooling data with patients from cohort 4 of Phase Ib portion for safety and for efficacy analysis, unless otherwise specified.

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

All patients who enrolled in the study will be included in the ITT population used for efficacy analyses.

4.1.2 Safety Population

All patients who enrolled in the study and received any amount of venetoclax or R-CHOP and/or G-CHOP will be included in the safety population used for safety analyses. Data from patients who receive R-CHOP or G-CHOP will be summarized by dose cohort and by phase separately, including a group of those who have not received any venetoclax.

4.1.3 Pharmacokinetic Evaluable Population

All patients who enrolled in the study and received any amount of venetoclax or R-CHOP/G-CHOP will be included in the PK evaluable population used for PK analyses.

4.1.4 Double Expressor Diffuse Large B-Cell Lymphoma

DE population is defined for the purpose of the primary efficacy and safety analyses, respectively, as 800 mg venetoclax in ITT patients with DLBCL who are co-expressing BCL-2 and c-MYC and therefore positive for BCL-2 and c-MYC IHC according to the Ventana IHC investigational-use-only assay. DE will be scored as described in Appendix 6 by a central laboratory.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients who are enrolled will be tabulated by treatment group, center, and country. Major eligibility violations and major protocol deviations will be listed or summarized if summary table is deemed appropriate. Patient disposition and reasons for study discontinuation will be summarized by treatment group for all enrolled patients (ITT). Duration of follow-up will also be assessed.

4.3 ANALYSIS OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Descriptive summaries will be provided for all baseline characteristics. Demographic and baseline characteristics that will be summarized by treatment group, dose cohort and phase for ITT population include but not limited to gender, age at consent (continuous and categorical), race, ethnicity, height, weight at baseline, body surface area, Eastern Cooperative Oncology Group (ECOG) Performance Status at screening, Ann Arbor staging at screening, bone marrow involvement at baseline, tumor bulk at baseline (lymph mass $\geq$10 cm), prior lymphoma history (for phase I), prognostic biomarkers (e.g., BCL-2 and c-MYC status by IHC and by FISH), DLBCL genotypic subtypes (e.g., ABC, GCB), IPI score, confirmed diagnosis to start of treatment, and geographic region.

The number of non-missing observations, mean, median, standard deviations, minimum, and maximum values of the continuous variables will be summarized. Percentages of patients within each subgroup of categorical variables will be provided.

If country policy prohibits the collection of race and/or age information, patients will appear in the missing category of summary table.

4.4 EFFICACY ANALYSIS

4.4.1 Primary Analysis

The primary efficacy endpoint, PET/CT-CR (modified Lugano) at end of treatment based on IRC assessment will be assessed for DE and ITT patients. Patients who do not have available end of treatment PET-CT or CT-CR assessment, or whose PET-CT assessment result is not evaluable at end of treatment will be counted as non-responders in the primary efficacy analysis. DE population PET/CT-CR (modified Lugano) rate will be defined as the proportion of patients with a PET/CT-CR in the DE population.

The primary analysis of PET/CT-CR rate will be performed in a frequentist setting with use of a one-sample exact test to test the superiority of venetoclax+R-CHOP over R-CHOP historical control response rate in the DE population (i.e., to test H_0: $P_E \leq P_C$ versus H_A: $P_E > P_C$, where P_E is the response rate of venetoclax+R-CHOP Phase II patients with DE DLBCL and P_C is the response rate of baseline PET evaluable DE within stability window, IPI 2–5 patients receiving R-CHOP in GOYA [Study BO21005, see Appendix 2]). 95% CIs of response rate for venetoclax+R-CHOP will be provided Efficacy is established if the PET/CT-CR rate in the venetoclax+R-CHOP DE population is observed to be significantly different from historical control in Phase II DE population. Historical control response rates for the ITT population will be also be based on results from the GOYA study R-CHOP arm with baseline evaluable PET and IPI score 2–5.

4.4.2 Sensitivity Analysis of the Primary Analysis

4.4.2.1 Sensitivity Analysis Using Analysis Method Adjusting for Potential Baseline Imbalance

Sensitivity analyses will be conducted with use of propensity score based methods that include the double robust (DR) method proposed by Robin (Bang and Robins 2005), to adjust for potential baseline imbalance between venetoclax+R-CHOP and the historical control R-CHOP. The double robust estimator combines inverse weight of propensity score as a covariate into the outcome logistic regression model that incorporates the important baseline prognostic factors including age, gender, body mass index, lactate dehydrogenase, IPI high (4 and 5) versus low, ECOG ≥2 versus <2, and stage IV versus stage I, II, and III.

Specifically, if $u(Z, X) = g(\tilde{\alpha} + \tilde{\beta}' X)$ is an outcome regression model where X is the vector of selected baseline covariates, and $e(X, \hat{\zeta})$ is the propensity score (i.e., the probability of receiving the treatment given the covariates, estimated from the propensity score model), then the DR estimator of mean response rate in venetoclax+R-CHOP treated patients is:

$$\tilde{\mu}_{DR}(Z = 1, X) = g(\tilde{\alpha} + \tilde{\beta}' X + \tilde{\eta} * [1/e(X, \hat{\zeta})])$$

The DR estimator of mean response rate in historical R-CHOP treated patients is:

$$\tilde{\mu}_{DR}(Z = 0, X) = g(\tilde{\beta}' X + \tilde{\eta} * [1/(1 - e(X, \hat{\zeta}))])$$

and the response rate difference is simply estimated as:

$$\tilde{\Delta}_{DR} = n^{-1} \sum_{i=1}^{n} \{\tilde{\mu}_{DR}(Z = 1, X) - \tilde{\mu}_{DR}(Z = 0, X)\}$$

Bootstrapped 95% CIs will be provided for the DR estimate of the difference in response rate.

Bayesian posterior probability (see Appendix 5) that venetoclax + R-CHOP has a 15% higher response rate than historical control will also be provided.

4.4.2.2 Sensitivity Analysis for Different Populations

The following sensitivity efficacy analyses will also be conducted for PET/CT-CR (modified Lugano):

- To evaluate the potential impact of missing data on the estimation of PET/CT-CR (modified Lugano), a sensitivity analysis will be done in the safety population (i.e., Patients who did not start treatment thus do not have available PET and/or CT assessment at the end of treatment will be excluded; however, for any reason discontinued patients who are treated will be included).
- To evaluate the potential impact of missing venetoclax on the estimation of PET/CT-CR (modified Lugano), another sensitivity analysis will be done in the DLBCL population who received at least one venetoclax dose and who have available PET-CT assessment at the end of treatment with protocol allowed assessment window.

Response proportions will be presented with 95% Clopper and Person (1934) CIs.

4.4.3 Secondary Analyses

PET/CT-CR (modified Lugano) rate and PET/CT-CR (Lugano) rate as assessed by investigator, CT-CR rate and OR (PET) rate as assessed by investigator and by IRC (only available for Phase II portion and 5 patients with DLBCL in Phase Ib Arm A cohort 4) will be analyzed for ITT patients and patients with DE DLBCL by treatment arm and dose cohort. Proportions will be presented with 95% CIs with use of the method of Clopper and Person (1934).

PFS and OS will be presented using Kaplan-Meier plots separately by treatment group and dose cohort for the ITT and the DE DLBCL ITT population. Median PFS and OS as well as 95% CI will be estimated if reached, otherwise, these will be summarized with use of the 1-year, 2-year, and if mature enough 3-year rates by Kaplan-Meier method, with 95% CIs calculated via Greenwood formula.

DOR will be analyzed according to the same methods as PFS and OS, for patients who are PET/CT CR or OR at end of treatment.

4.4.4 Exploratory Analyses

Key efficacy endpoint analysis will be repeated in biomarker subgroups as listed in Section 2.2.3, including BCL-2-high by IHC, c-MYC high by IHC, BCL-2 and c-MYC translocation by FISH, GCB, ABC, and others.

MRD response rate (defined as proportion of patients with negative MRD at the end of treatment whose baseline MRD is positive) and other timepoints will be assessed in ITT in DE and other relevant biomarker subgroups. The MRD population will be defined as

patients with at least one calibrating clone, and who are MRD positive at baseline. Cases where no post-baseline MRD assessment is available will be considered MRD non-responders.

Analysis of biomarker and exploratory endpoints as defined in the protocol will be provided in separate reports.

4.5 SAFETY ANALYSES

Safety will be assessed through summaries of adverse events, serious adverse events, deaths, and adverse events of special interest (include Grade 4 neutropenic fever, Grade $\geq$3 infusion-related reactions [IRRs] to rituximab, and tumor lysis syndrome [TLS]). Summaries of changes include shift tables when appropriate from screening assessments in laboratory test results, ECGs, measurement of vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation will be included.

The safety analyses will be performed based on the safety population.

Safety analysis from Phase Ib will be grouped by treatment arm and venetoclax dose cohort (i.e., 200 mg, 400 mg, 600 mg, and 800 mg). Safety analysis for Phase II will be presented separately.

4.5.1 Exposure to Study Medication

Information on each study drug administration will be summarized by treatment duration, dose intensity (percentage of the planned dose), and cumulative dose. Treatment exposure will be summarized by each study medication given at each cycle. Descriptive analysis includes number of patients, mean, standard deviation, median, minimum, and maximum.

Listings and summary tables for patients discontinue from study treatment will be reported.

4.5.2 Dose Modifications and Dose Intensity

Both Dose Modification and Dose Intensity Evaluations will be performed by venetoclax dose groups (200-, 400-, 600-, and 800-mg), and treatment (R, C, H, O, P, R–CHOP, V), unless otherwise specified.

4.5.2.1 Dose Modifications

Dose modifications include both dose delays and/or dose reductions.

Dose delays or reductions for R–CHOP combined will be flagged yes if dose delays or reductions occurred to any of R, C, H, O, or P.

4.5.2.2 Dose Intensity

The evaluation of relative dose intensity will be performed at the patient level.

Two kinds of dose intensity definition will be explored and calculated:

$$\frac{\sum actual\_dose}{\sum planned\_dose} \quad \text{vs.} \quad \frac{\frac{\sum actual\ dose}{total\ time\ on\ treatment}}{\frac{\sum planned\ dose}{planned\ time\ on\ treatment}}$$

Actual dose:

- Overall: actual cumulative dose until end of treatment or cutoff, whichever occurs first.

Planned dose:

- Overall: dose regimen should be per protocol, see details below in italic font. Calculation of planned dose depends on the last cycle of that patient until the data cutoff date.

  For infusion drugs:

  Rituximab infusion (375 mg/m^2) or obinutuzumab (1000 mg) on Day 1 (also Day 8 and 15 for Cycle 1)

  Cyclophosphamide 750 mg/m^2 administered intravenously on Day 1

  Doxorubicin 50 mg/m^2 administered intravenously on Day 1

  Vincristine 1.4 mg/m^2 administered by intravenous push on Day 1 with a cap of 2.0 mg

  Note: For planned dose which is based on body surface area, baseline body surface area will be used to calculate the planned dose.

  For oral drugs:

  Venetoclax Cycle 1 Days 4–21 or Cycles 2–8 Days 1–21 for Cohort 1

  Venetoclax Cycle 1 Days 4–10 or Cycles 2–8 Days 1–10 for Cohort 2–4

  Prednisone 100 mg/day orally on Days 1–5

Total (actual) time on treatment:

- Overall: last treatment date − first treatment date + 1

Planned time on treatment:

- Overall: based on treatment disposition and patient's last cycle until the data cutoff date. Planned time is protocol specified cycle length. In general 21 days per cycle.

  If a patient discontinued treatment, use actual time on treatment

  If a patient completed treatment:

  Use actual time on treatment if actual time on treatment is within 2 day time window compared to planned time on treatment.

Use calculated planned time on treatment if actual time on treatment exceeds 2 day time window.

If a patient neither discontinued nor completed, calculate planned time until the data cutoff date.

Dose intensities will be summarized by the following categories: $<$80%, 80%–84%, 85%–89%, and $\geq$90% for each formula.

4.5.3 Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). All adverse events and routine laboratory parameters will be assessed according to the NCI CTCAE v4.0 grading system. For the Phase Ib portion, 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 unevaluable for DLT and MTD assessments and will be replaced.

All recorded adverse events will be listed by treatment arm, study site, patient number, and schedule. The most extreme intensity will be used for reporting. All adverse events occurring on or after the first study treatment will be summarized by body system, NCI CTCAE grade, and relation to study treatment. In tables showing the overall incidence of adverse events, patients who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency and the adverse event with the most extreme severity will be included.

Selected events of special interest (e.g., Grade 4 neutropenic fever, Grade $\geq$3 IRRs to rituximab or obinutuzumab, and Grade $\geq$4 TLS) will be summarized by treatment arm and dose cohort and listings will be provided. Hepatitis B reactivation will be followed and summarized as an adverse event of particular interest.

Adverse events leading to dose interruptions (including dose delay and dose modifications), early treatment discontinuation, or early study withdrawal will be summarized by treatment arm.

All serious adverse events will be listed separately and summarized. Deaths reported during the study treatment period and those reported during follow-up after patient discontinuation will be listed.

4.5.4 Laboratory Data

Laboratory measurements and change from baseline will be summarized by treatment arm, where baseline measurement is defined as the last valid measurement before first dose of any study medication. The summary of TLS-related measurements (including uric acid, potassium, inorganic phosphorus, and calcium) and change from baseline will

be provided. In addition, laboratory measurement from individual patients who developed TLS by Howard criteria (regardless of TLS adverse event reporting by site) during the study will be presented in a listing. Important hematology parameters, such as absolute lymphocyte count, ANC, hemoglobin, hematocrit, and WBC will be categorized according to NCI CTCAE version 4.0 grading with values within, above, or below the normal range comparing baseline to subsequent assessment by treatment arm and overall. Shift tables will be generated to show the number and percentage of patients at baseline versus postbaseline observations.

The laboratory measurement for hepatitis B DNA polymerase chain reaction, including hepatitis B surface antigen, anti-hepatitis B core antibody, and hepatitis C antibody serology (also hepatitis C virus and RNA by polymerase chain reaction if the patient is hepatitis C virus antibody positive) will be listed.

4.5.5 Vital Signs

Vital signs, including absolute value and change from baseline, will be summarized over time by treatment arm without any imputation for missing data.

ECG data at screening visit will be summarized. Abnormal physical examination at screening visit will be listed.

4.6 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 with the use of non-compartmental methods, and 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)
- T_{max}
- C_{max}
- C_{min}

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 CL/F, V, and $T_{1/2}$ may also be calculated as data allow.

Additional analyses, such as population PK and/or pharmacodynamics analysis, may be performed to characterize the pharmacokinetics and potential correlations of exposure with dose, demographics, pharmacodynamics, 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 biotransformed products of venetoclax.

4.7 MISSING DATA

For the response assessments, patients with no end of treatment response assessments (for any reason) will be considered non-responders.

For PFS, patients who do not have documented disease progression and have not died will be treated as censored observations on the date of the last tumor assessment. If no tumor assessments were performed after the baseline visit, PFS will be censored at the time of enrollment.

For overall survival, patients who have not died at the time of analysis will be censored at the last date of known contact.

Patients who could not have DE status determined (due to missed sample collection or technical failure of assay) will be excluded from efficacy analysis of DE patients.

4.8 INTERIM ANALYSES

The safety interim analysis will occur when 20 patients in Phase II in the venetoclax + R-CHOP arm complete 2 cycles of combination therapy and will enable formal safety review of adding venetoclax to R-CHOP.

Besides the safety interim analysis, an additional two efficacy interim analyses will be performed after approximately 40 and 70 patients complete their end of treatment response assessments, respectively. Additional interim analyses may be conducted to guide future development before or after primary analysis.

A predictive probability design (an extension to Lee and Liu 2008) will be used to guide early decision-making for futility or efficacy by comparison of CR rates in the venetoclax + R-CHOP arm to R-CHOP historical control in the Bayesian setting. Predictive probability at interim time points will be estimated to show the chance that venetoclax + R-CHOP is efficacious or futile at the end of the study given evidence from ongoing data. However, there will be no stopping for efficacy as additional safety and efficacy data would be required to plan for a Phase III study.

5. REFERENCES

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Appendix 1
Protocol Synopsis (Study GO27878)

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IB/II, OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF VENETOCLAX (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)
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)

Appendix 1
Protocol Synopsis (Study GO27878) (cont.)

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

Appendix 1
Protocol Synopsis (Study GO27878) (cont.)

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.

Appendix 1
Protocol Synopsis (Study GO27878) (cont.)

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 ^{18}F-fleurodeoxyglucose (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)

Appendix 1
Protocol Synopsis (Study GO27878) (cont.)

- 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):

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

  Or, if serum creatinine is in μmol/L:

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

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

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

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

  PTT or aPTT $>1.5 \times$ 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 $\geq$3 infusion-related reactions (IRR) to rituximab or obinutuzumab, and Grade $\geq$4 tumor lysis syndrome (TLS).
- Change in clinical laboratory test 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.

Appendix 1
Protocol Synopsis (Study GO27878) (cont.)

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/m^2 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/m^2 on Cycle 1 Day 1, 250 mg/m^2 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/m^2 administered intravenously on Day 1
- Doxorubicin 50 mg/m^2 administered intravenously on Day 1
- Vincristine 1.4 mg/m^2 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 ≤ 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.

Appendix 1
Protocol Synopsis (Study GO27878) (cont.)

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.

Appendix 1
Protocol Synopsis (Study GO27878) (cont.)

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.

Appendix 2
Protocol Synopsis (Study BO21005)

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, OPEN-LABEL, RANDOMIZED TRIAL COMPARING THE EFFICACY OF GA101 (RO5072759) IN COMBINATION WITH CHOP (G-CHOP) VERSUS RITUXIMAB AND CHOP (R-CHOP) IN PREVIOUSLY UNTREATED PATIENTS WITH CD20-POSITIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)**
PROTOCOL NUMBER:	BO21005
VERSION NUMBER:	5
EUDRACT NUMBER:	2010-024194-39
STUDY DRUG:	Obinutuzumab (GA101, RO5072759)
PHASE:	III
INDICATION:	CD20-Positive Diffuse Large B-Cell Lymphoma
IND NUMBER:	104405
SPONSOR:	Genentech, Inc. (U.S.) F. Hoffmann-La Roche, Ltd (ex-U.S.)

Objectives

Primary Objective

The primary objective of this study is to demonstrate superiority in progression-free survival (PFS) with obinutuzumab plus chemotherapy (G-CHOP) compared with rituximab plus chemotherapy (R-CHOP) in previously untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL), based on investigator-assessed PFS.

Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate and compare overall survival (OS) between the two arms treated with the combination of G-CHOP or R-CHOP
- To evaluate and compare the overall response rate and complete response (CR) rate after the end of treatment between the two arms, as assessed by the investigator, with and without ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)
- To evaluate and compare PFS between the two arms, as assessed by the Independent Review Committee (IRC)
- To evaluate and compare the overall response rate and CR rate based on the IRC assessment after the end of treatment between the two arms, with and without FDG-PET
- To evaluate and compare event-free survival (EFS) between the two arms, as assessed by the investigator
- To evaluate and compare disease-free survival (DFS), duration of response (DOR), and time to next anti-lymphoma treatment (TTNALT) between the two arms

Appendix 2
Protocol Synopsis (Study BO21005) (cont.)

- The DFS and DOR will be based on the investigator's assessment.
- To evaluate and compare the safety profiles of patients treated with the combination of G-CHOP or R-CHOP
- To assess patient-reported outcomes (PROs) in both arms
- To evaluate medical resource utilization in both arms
- For Japanese patients only: to characterize the pharmacokinetics of obinutuzumab in combination with CHOP

Study Design

This is a Phase III, multicenter, open-label, randomized trial comparing the efficacy of G-CHOP versus R-CHOP in previously untreated patients with CD20-positive DLBCL. Approximately 1400 patients from approximately 300 centers in 30–40 countries will receive eight 21-day cycles of obinutuzumab or rituximab combined with six or eight cycles of standard CHOP chemotherapy. Patients randomized to the obinutuzumab arm will receive an additional two doses on Days 8 and 15 of Cycle 1. This will allow all patients to achieve trough levels of 300–600 μg/mL.

Centers must choose prior to study start whether they plan to administer six or eight cycles of CHOP chemotherapy. This will allow for stratification by the number of planned chemotherapy cycles.

Patients will be randomized in a 1:1 ratio to receive G-CHOP or R-CHOP, with patients stratified on the basis of the number of planned chemotherapy cycles (6 vs. 8 cycles of CHOP), International Prognostic Index (IPI) score (low/low–intermediate [excluding patients with an IPI score of 0 without bulky disease], high-intermediate, or high-risk), and region (Western Europe, Eastern Europe, South and Central America, North America, Asia, and others). The control arm of the study will receive standard of care treatment with R-CHOP. No crossover to the experimental arm is allowed.

Patients will be assessed for disease response by the investigator using regular clinical and laboratory examinations and computed tomography (CT) scans, according to a modified version of the Revised Response Criteria for Malignant Lymphoma. Best response will be evaluated at the end of eight cycles of obinutuzumab or rituximab, or sooner in the event that a patient discontinues early. In patients for whom FDG-PET scans are obtained (FDG-PET scans are mandatory at sites where a PET scanner is available), a separate response assessment will incorporate FDG-PET scan results.

After completion of therapy, all patients will be followed at clinic visits conducted every 3 months for 2 years, then every 6 months until Month 60, and then annually; after 5 years, patients will be followed by telephone contact until the end of the study, which is estimated to be approximately 78 months after the first patient is enrolled (for the list of study assessments, see Appendices A-1 and A-2). At each visit up to the Year 5, Month 60 assessment (or until disease progression if it occurs before 5 years), assessments will include physical examination, standard hematologic and biochemistry assessments, vital signs, weight, liver and spleen size, and B-symptoms (e.g., weight loss, night sweats, or fever). After 5 years, patients will be followed only for survival and initiation of a new anti-lymphoma therapy by telephone contact until study termination or consent withdrawal by patient. After disease progression, patients will be followed for survival only (by telephone contact) and for applicable adverse event reporting, initiation of a new anti-lymphoma therapy, and two PRO assessments.

Patients who terminate study treatment early without progressive disease (PD) will complete their Early Study Treatment Termination visit and then will be followed until disease progression and survival as per Appendix A-2 for progression new anti-lymphoma therapy, and overall survival.

Patients who discontinue the protocol-defined treatment and need to start a new anti-lymphoma therapy (NALT) in the absence of disease progression (e.g., if wrong diagnosis at screening and

new diagnosis requires a change of treatment) will be followed for disease progression and survival.

Patients who terminate study treatment early because of PD will go into the follow-up per Appendix A-2 schedule and will be followed for new anti-lymphoma therapy and overall survival.

CT scans will be obtained at baseline and after Cycles 4 and 8 of study treatment. During the follow-up period, CT scans will be performed every 3 months (i.e., Months 3, 6, 9, 12, 15, 18, 21, and 24) until the end of Year 2 of follow-up (2.5 years after the first dose) in accordance with study (clinic) visits and will include the neck (if involved at baseline), chest, abdomen, and pelvis. During Years 3 and 4 of follow-up, CT scans will only be obtained of sites with prior involvement and will be repeated every 6 months (at Months 30, 36, 42, and 48) and again at Year 5, Month 60 of follow-up. If disease in other areas is suspected, additional areas should be imaged. FDG-PET scans (which are mandatory at sites where a PET scanner is available) will be performed at screening and 6-8 weeks after the last study treatment.

Safety will be evaluated by monitoring all adverse events, serious adverse events, and abnormalities identified through physical examinations, vital signs, and laboratory assessments. Such events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 4.0). Laboratory safety assessments will include routine monitoring of hematology and blood chemistry, and tests of immunologic parameters. In addition, tests for the presence of human anti–human antibodies (HAHAs) will be performed for a subset of 100 patients treated in the G-CHOP arm.

For a subset of Japanese patients only, samples for assessment of serum obinutuzumab concentrations will be collected from up to 40 patients enrolled and treated with G-CHOP. PK analysis of obinutuzumab will be performed to compare PK profiles between Japanese patients and non-Japanese patients on the basis of historical data.

Outcome Measures

Primary Efficacy Outcome Measure

The primary endpoint of this study is investigator-assessed PFS, which is defined as the time from randomization to the first occurrence of progression or relapse, using a modified version of the Revised Response Criteria for Malignant Lymphoma, or death from any cause.

While the primary efficacy endpoint is investigator-assessed PFS, PFS based on IRC assessment will also be analyzed to support the primary analysis. In the United States, IRC-assessed PFS will be the basis for regulatory decisions.

Secondary Outcome Measures

Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- Overall survival, defined as the time from the date of randomization to the date of death from any cause. Overall survival for patients who are not reported to have died at the time of the analysis will be censored at the date at which the patient was last known to be alive, as documented by the investigator.
- Event-free survival (EFS), defined as the time from randomization to disease progression or relapse, death from any cause, as assessed by the investigator, or initiation of any NALT. If the specified event (disease progression or relapse, death, initiation of an NALT) does not occur, EFS will be censored at the date of last tumor assessment. For patients without an event who have not had post-baseline tumor assessments, EFS will be censored at the time of randomization.
- Overall response rate (ORR) at the end of treatment, as assessed by the investigator, with and without FDG-PET. The overall response rate is defined as the percentage of patients with CR or partial response (PR) at the end of treatment. All other cases are designated non-responders.

- CR rate at the end of treatment, defined as the percentage of patients with CR at the end of treatment, as assessed by the investigator, with and without FDG-PET.
- Overall response (CR or PR) at the end of the treatment, as assessed by the IRC, with and without FDG-PET
- CR at the end of the treatment, as assessed by the IRC, with and without FDG-PET
- Disease-free survival (DFS), defined as the time from the date of the first occurrence of a documented CR to the date of disease progression, relapse or death from any cause (PFS), as assessed by the investigator, for the subgroup of patients with a best overall response (BOR) of CR. Patients who have had no documented disease progression, relapse, or have not died after CR, will be censored at the last disease assessment date.
- Duration of response (DOR), defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse or death from any cause (PFS), as assessed by the investigator for the subgroup of patients with a BOR of CR or PR. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the duration of response will be censored on the date of last disease assessment.
- Time to next anti-lymphoma treatment (TTNALT) is defined as the time from the date of randomization to the start date of the next anti-lymphoma treatment or death from any cause. For patients who have not received the next anti-lymphoma treatment or have died prior to the time of analysis, TTNALT will be censored at the date at which the patient was last known to be alive without having received NALT.
- Medical resource utilization, including the number of hospitalizations, length of hospital stay, types of subsequent drug therapies, and medical and surgical procedures and treatments (i.e., blood transfusions, bone marrow transplantation, or stem-cell transplantation)

Safety Outcome Measures

The safety and tolerability of obinutuzumab in combination with CHOP will be assessed using the following primary safety outcome measures:

- Incidence, nature, and severity of adverse events and serious adverse events with G-CHOP versus R-CHOP administration
- Changes in vital signs, physical findings, and clinical laboratory test results during and following study treatment administration
- Incidence of HAHAs in the first 100 patients treated in the G-CHOP arm

Patient-Reported Outcome Measures

The quality-of-life measures that will be used to evaluate PROs are as follows:

- Change from baseline in health-related PROs to the end of study, as assessed using the Functional Assessment of Cancer Therapy–Lymphoma subscale
- Descriptive results of the Euro–Quality of Life 5D data during different periods of the study
- Change from baseline in each of the 14 domains of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

Pharmacokinetic Outcome Measures (for a Subset of Japanese Patients Only)

The PK outcome measure for this study is as follows:

- PK profile (i.e., plasma concentration–time profiles, pre-dose trough concentrations, and clearance rates) of obinutuzumab in the G-CHOP arm

Appendix 2
Protocol Synopsis (Study BO21005) (cont.)

Safety Plan

This trial is designed to allow for early termination or a modification of the protocol for safety concerns, based on the advice of an independent data monitoring committee (IDMC) for safety or futility concerns. The IDMC will be incorporated into the study to review safety data, including adverse events of special interest, on a regular basis. In addition, the dose intensity of the CHOP chemotherapy regimen will be included as part of the safety monitoring. The IDMC will meet 1 month after the first patient is enrolled and then approximately every 2 months until 100 patients have completed two cycles of immunochemotherapy (with approximately 50 patients in each arm). Thereafter, the IDMC will meet approximately every 6 months until the interim analysis and subsequently at a frequency determined by the IDMC and the Sponsor. Both the Sponsor and the IDMC can request ad-hoc meetings for any reason. Following each meeting, the IDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of data review. In exceptional cases, the IDMC may recommend stopping the study for safety reasons. The Sponsor will make the final decision for continuation or discontinuation of the study on the basis of the IDMC's recommendation.

In addition, the IDMC will meet to review the efficacy and safety data from two formal event-driven interim futility and efficacy analyses during the study.

Risks Associated with Obinutuzumab Therapy

To date, the commonly experienced infusion-related reactions (IRRs) have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, and fatigue, as well as other symptoms.

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, v3.0, 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 chronic lymphocytic leukemia [CLL]) may be a predisposing factor for the development of IRRs.

Cases of tumor lysis syndrome 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 $\geq 25 \times 10^9$/L (particularly patients with B-cell CLL and mantle cell lymphoma), are at increased risk for tumor lysis syndrome and severe IRRs.

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of granulocyte colony-stimulating factors (G-CSF) has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G-CSF is allowed for treatment of neutropenia in this study. Primary prophylaxis with G-CSF is recommended according to the American Society of Clinical Oncology (ASCO), EORTC, and European Society for Medical Oncology (ESMO) guidelines, namely for patients who are ≥ 60 years old and/or with co-morbidities. The use of G-CSF is strongly recommended in Cycle 1 for all patients treated with G-CHOP.

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. Based on the available evidence to date the greatest risk of hemorrhage in obinutuzumab-treated patients is observed in the first cycle. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients treated with

concomitant medication, which 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; 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) according to institutional practice is at the discretion of the treating physician.

Based on its anticipated mode of action, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

Reactivation of hepatitis B as well as other serious viral infections (e.g., infections caused by cytomegalovirus, Varicella zoster virus, herpes simplex virus, John Cunningham virus (JCV), and hepatitis C virus) that were new, reactivation, or exacerbation, 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. Particular attention should be given to patients who have previously received significant immunosuppressive treatment such as high-dose chemotherapy and stem-cell transplant.

Cases (including fatal) of JCV infection that resulted in progressive multifocal leukoencephalopathy (PML, destructive infection of oligodendrocytes of the CNS white matter) have been reported in patients treated with anti-CD20 therapies, including rituximab and GA101.

The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are very unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) can occur.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture to quantify DNA of JCV in the cerebrospinal fluid.

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

Risks Associated with Rituximab Therapy

Patients treated with rituximab in combination with chemotherapy are at risk for IRRs. Fatal infusion reactions within 24 hours of rituximab infusion can occur; approximately 80% of fatal reactions occurred with the first infusion. Severe reactions to rituximab typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Patients may be at risk for tumor lysis syndrome. With rituximab treatment, acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of rituximab in patients with non-Hodgkin’s lymphoma. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden confers a greater risk of tumor lysis syndrome. For patients with evidence of tumor lysis syndrome, rituximab should be discontinued and the patient treated as clinically indicated.

Hepatitis B virus reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab treatment and approximately 1 month after the last dose.

Patients with chronic hepatitis B (i.e., hepatitis B surface antigen [HbsAg] positive) viral infection are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg negative and hepatitis B core

antibody positive) are at a lower risk for reactivation. In a study of 51 hepatitis B carriers with DLBCL who received rituximab, 12% of patients developed evidence of reactivation.

Rare cases of PML have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications. The diagnosis of PML in any patient treated with rituximab is extremely rare but should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem-cell transplant. Most cases of PML were diagnosed within 12 months of the patients' last infusion of rituximab.

Angina and cardiac arrhythmias have occurred with rituximab treatment and can be life threatening. Treatment with CHOP chemotherapy is a known risk factor for cardiotoxicity, and to mitigate this risk, patients will be required to undergo assessments of left ventricular ejection fraction at baseline, at the end of Cycle 6, and at the end of treatment.

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following the completion of rituximab-based therapy. New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, Varicella zoster virus, West Nile virus, and hepatitis B and C.

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens–Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following rituximab exposure.

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In post-marketing reports of rituximab, the mean time to documented gastrointestinal perforation was 6 days (range, 1–77) in patients with non-Hodgkin's lymphoma.

Risks Associated with CHOP Chemotherapy

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

Study Treatment

Patients will receive treatment with one of two immunochemotherapy regimens:

- G-CHOP (investigational arm): CHOP chemotherapy combined with obinutuzumab
- R-CHOP (control arm): CHOP chemotherapy combined with rituximab

In the investigational arm, obinutuzumab will be administered by intravenous (IV) infusion at an absolute (flat) dose of 1000 mg on Day 1 of each 21-day cycle for 8 cycles. During Cycle 1, obinutuzumab will also be infused on Days 8 and 15. Administration of obinutuzumab on days when both obinutuzumab and CHOP are to be given should be completed for at least 30 minutes before chemotherapy administration is started.

CHOP chemotherapy may be given on the next day after obinutuzumab administration if the duration of the obinutuzumab infusion necessitates administration of the CHOP infusion the next day. CHOP chemotherapy will be given for a maximum of 6 or 8 cycles, as described in Section 4.5.3.a and Table 5. If only 6 cycles of CHOP chemotherapy are to be administered, Cycles 7 and 8 of obinutuzumab will be given as monotherapy on an every-21-day schedule.

Rituximab will be administered prior to CHOP. Once the rituximab infusion is completed, patients are to be observed for 30 minutes prior to the start of CHOP administration. For patients who experience an adverse event during a rituximab infusion, administration of rituximab and CHOP chemotherapy may be continued on the following day if required. Empiric dose adjustment for obese patients (defined as a body mass index $\geq$30, as measured in kilograms per meter squared) may be implemented per institutional guidelines. There will be no dose modification for changes in weight unless a patient's weight increases or decreases by

> 10% from his or her weight from screening. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments.

CHOP chemotherapy may be administered on the next day if administration of rituximab has been split or CHOP cannot be administered on the same day. If CHOP chemotherapy is not given at Cycles 7 and 8, rituximab will be administered as monotherapy.

For dosage and administration instructions for CHOP chemotherapy, see Section 4.3.4.

Concomitant Therapy and Clinical Practice

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the study entry evaluation and the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF). Patients who are receiving oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Central nervous system prophylaxis should be given according to institutional practice and its use documented on the eCRF.

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.

The use of G-CSF is allowed for treatment of neutropenia. Primary prophylaxis with G-CSF is recommended according to ASCO, EORTC, and ESMO guidelines for patients who are ≥ 60 years old and/or with co-morbidities. The use of G-CSF prophylaxis is strongly recommended in Cycle 1 for all patients treated with G-CHOP.

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

Pre-planned radiotherapy (i.e., radiation that was planned before randomization to be given at the end of study treatment) may be administered to initial sites of bulky or extranodal disease according to institutional practice. If indicated, pre-planned radiotherapy should be administered within 8 weeks after the last antibody cycle (Day 1 of the last cycle) and radiation should start after all “End of treatment assessments” including complete response assessments are completed. Any radiotherapy should be pre-planned by the center and documented prior to randomization and then entered in the eCRF once the patient is randomized. For patients receiving pre-planned irradiation, response assessment will be performed prior to the start of radiotherapy. All unplanned radiotherapy administered to patients at the end of treatment will be considered as a new anti-lymphoma treatment.

Treatment with other concomitant anti-tumor agents not defined in this protocol as study treatment, radiotherapy, or other concurrent investigational agents of any type will result in withdrawal of patients from study treatment; however, patients will be followed as described in Section 4.5.4.

Use of cytotoxic chemotherapy (other than CHOP), immunotherapy, hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate), any therapies (other than intrathecal central nervous system prophylaxis) intended for the treatment of lymphoma whether European Medicines Agency or Food and Drug Administration approved or experimental (outside of this study), radiotherapy, and pre-phase therapy (with the use of chemotherapeutic or anti-lymphoma agents) is prohibited. Use of prednisone alone with maximum dose of 100 mg/day (or equivalent dose of other steroids alone), for ≤ 5 days for symptom relief after the staging and radiology assessments are completed and before Cycle 1 Day 1 is allowed.

Appendix 2
Protocol Synopsis (Study BO21005) (cont.)

Statistical Methods

Primary Efficacy Analysis

The primary analysis population for efficacy is the intent-to-treat population, defined as all randomized patients. Patients will be analyzed according to the treatment arm to which they were randomized.

The primary efficacy endpoint is PFS, as determined by the investigator, defined as the time from the date of randomization until the first occurrence of disease progression, relapse, or death from any cause. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of last disease assessment. If no tumor assessments were performed after the baseline visit, PFS will be censored at the time of randomization.

While the primary efficacy endpoint is investigator-assessed PFS, PFS based on IRC assessments will also be analyzed to support the primary analysis. In the United States, IRC-assessed PFS will be the basis for regulatory decisions.

The primary analysis of the study will test the equality of PFS distributions in the obinutuzumab + CHOP (G-CHOP) and rituximab + CHOP alone (R-CHOP) arms:
H_0: $PFS_{G\text{-}CHOP} = PFS_{R\text{-}CHOP}$ versus H_1: $PFS_{G\text{-}CHOP} \neq PFS_{R\text{-}CHOP}$

Treatment comparison will be made using a two-sided level 0.05 stratified log-rank test. While randomization is stratified by region, the primary and secondary stratified efficacy analyses will omit this factor in order to avoid loss of efficiency. Therefore, the randomization stratification factors to be used in the efficacy analyses are IPI score (low/low–intermediate [excluding patients having an IPI score 0 without bulky disease], high–intermediate, or high-risk) and planned number of CHOP cycles (8 vs. 6 cycles, see Section 3.1). The Kaplan–Meier method will be used to estimate the PFS distribution for each treatment arm. The Kaplan–Meier curve will provide a visual description of the differences across treatment arms. Estimates of the treatment effect will be expressed as hazard ratios using a stratified Cox proportional-hazards analysis, including 95% confidence limits. Median PFS is not expected to be reached in this study at the time of the primary analysis; hence, the 1-year, 2-year, and 3-year PFS rates will be used to describe PFS in addition to the hazard ratio.

Missing Data

For PFS, patients who do not have documented disease progression or have died will be treated as censored observations on the date of the last tumor assessment. If no tumor assessments were performed after the baseline visit, PFS will be censored at the time of randomization.

For OS, data from patients who do not have documented deaths will be censored on the last date they were known to be alive.

For the response endpoints, patients with no response assessments (for any reason) will be considered non-responders.

Determination of Sample Size

Approximately 1400 patients need to be recruited and randomized in a 1:1 ratio to the two treatment arms (R-CHOP and G-CHOP). The sample size considerations are based on the following assumptions:

- A two-sided log-rank test
- 80% power at the 5% significance level
- A 25% reduction in the risk of disease progression, relapse, or death (i.e., the PFS hazard ratio of G-CHOP over R-CHOP is 0.75)

- PFS in the control arm follows a piece-wise exponential distribution, with the hazard rate h(t) estimated using historical R-CHOP data as follows: h(t) = 0.0237 for t between 0 and 6 months; h(t) = 0.0414 for t between 6 and 9 months; h(t) = 0.0154 for t between 9 and 15 months;
  h(t) = 0.0094 for t between 15 and 21 months; h(t) = 0.0066 for t beyond 21 months.

  On the basis of this hazard rate assumption for the control arm and a hazard ratio of 0.75, the 3-year PFS rate is expected to improve from 60% to 68%. One-year, 2-year, and 3-year PFS rates will be provided as an alternative summary of the magnitude of treatment benefit because estimates of median PFS are not expected to be reached in either arm. Inference will be based solely upon the log-rank test and power calculations will be based on the hazard ratio.
- An annual dropout rate of 5%
- One planned futility analysis for PFS and one planned efficacy interim analysis for PFS (see the interim analysis plan for alpha- and beta-function spending)
- In addition, a futility analysis based on the CR rates at the end of treatment will be performed for the 200 randomized patients

Based on these assumptions, 405 PFS events are needed for the primary analysis. There will be a staggered recruitment in order to recruit the first 200 patients at a fewer number of sites (~80 sites) and then open up recruitment at all 250 sites following the IDMC meeting for the futility analysis based on CR rates. The maximum accrual rate will be approximately 48 patients per month, after the IDMC meeting plus 6 months of ramp up. The 1400 patients enrolled over 3 years and followed for an additional 7 months will provide 405 PFS events based on investigator assessment. The primary analysis will be performed once 405 investigator-assessed PFS events have been observed.

The PK assessment will apply to a subset of up to 40 Japanese patients receiving G-CHOP chemotherapy in this study. Data from 12 Japanese patients enrolled in a Phase I study (JO21900) with obinutuzumab are available; therefore, more than 52 patients will be analyzed in total. In addition, to compare the existing NCA parameters from Phase I/II obinutuzumab studies, 6 patients will undergo full sampling. This sample size is believed to be sufficient to compare the ethnic difference between Japanese patients and non-Japanese patients.

Interim Analyses

The IDMC will be used to evaluate efficacy and safety at three formal interim analyses, as well as periodic safety reviews, and to recommend if the trial should be stopped early. All summaries and analyses will be prepared by the Independent Data Coordinating Center and presented by treatment arm for the IDMC's review. Members of the IDMC will be external to the Sponsor and the study team and will follow a charter that outlines their roles and responsibilities.

Three interim analyses, two for futility and one for efficacy, are planned. The first interim analysis will be based on differences in end-of-treatment CR rates in the first 200 randomized patients. This interim analysis will be conducted once 200 patients have completed their end-of-treatment response assessment or have withdrawn prematurely. The IDMC may recommend that the study be stopped for futility if the observed difference in CR rates is $< 5\%$ in favor of G-CHOP (i.e., the CR rate needs to be $\geq 5\%$ higher on G-CHOP compared with R-CHOP).

The second interim analysis (PFS futility and safety analysis) will be conducted when approximately 33% of the required PFS events (134 of 405 total PFS events) have occurred. The IDMC may recommend that the study be stopped for futility if the observed PFS hazard ratio of obinutuzumab over rituximab is > 1 (futility boundary based on non-binding O'Brien–Fleming beta-spending function).

The third interim analysis (PFS efficacy analysis) will be conducted when approximately 70% of the required PFS events (284 of 405 total PFS events) have occurred. PFS will be tested at the

significance level determined using the O'Brien–Fleming alpha-spending function so that the overall type I error rate will be maintained at the 0.05 level. With 70% information, the alpha spending is 0.015.

Additional details of the interim analyses will be provided in the IDMC Charter and Statistical Analysis Plan.

Appendix 3 Schedule of Assessments

Study Period	Screening Period	Treatment Period															Follow-Up Period			Participation End
Cycles of Treatment Period		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	x [b]		x [b]
ECOG Performance Status	x																x	x		
Complete physical examination	x																			
Targeted physical examination							x		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		x
12-Lead ECG (in triplicate)	x																			
MUGA/Echocardiogram [e]	x																			
Clinical response assessment [f]							x		x		x			x		x	x	x		x
PET-CT scan & Response Assessment [g, h]	x [i]												x				x	x [j]		(x) [k]
Drug administration																				

Appendix 3 Schedule of Assessments (cont.)

Study Period	Screening Period	Treatment Period															Follow-Up Period			Participation End
Cycles of Treatment Period		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)	
Venetoclax (GDC-0199) [l]			x (Cycle 1 Days 4-10, and Cycles 2-8 Days 1-10)																	
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		

Appendix 3 Schedule of Assessments (cont.)

Study Period	Screening Period	Treatment Period															Follow-Up Period			Participation End
Cycles of Treatment Period		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)	
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]																		
Tumor biopsy for *BCL2* family expression by IHC	x [i, w]																x	x		
Tissue punch for TMAs (in Phase II only)	x [w]																			
PK sample for venetoclax (GDC-0199)	See Appendix 3 of protocol																			
PK sample for rituximab [m]	See Appendix 3 of protocol																			
PK sample for obinutuzumab [n]	See Appendix 3 of protocol																			
PK for CHOP components	See Appendix 3 of protocol																			
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		x [v]									x						x	x [aa]		

Appendix 3 Schedule of Assessments (cont.)

Study Period	Screening Period	Treatment Period															Follow-Up Period			Participation End
Cycles of Treatment Period		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)	
Phase II only																				
Optional Roche Clinical Repository Sample(s) [bb]		(x) [v]																		
Contacts for Survival Follow-up [cc]																			x	

Appendix 3 Schedule of Assessments (cont.)

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; 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 of protocol.

[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 4). 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 of protocol.

[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 of protocol.

[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.

Appendix 3 Schedule of Assessments (cont.)

[r] Serum chemistries listed in Section 4.5.1.5 of protocol.

[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 4
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.

Appendix 4
The Modified Lugano Classification: Revised Criteria for Response Assessment (cont.)

In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, and bone marrow), ^{18}F-fleurodeoxyglucose (FDG) uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

Appendix 4
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.

Appendix 4
The Modified Lugano Classification: Revised Criteria for Response Assessment (cont.)

Response	Site	PET-CT–Based Response	CT-Based Response
	Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase.
	Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal.
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	Not applicable
No response or stable disease		No metabolic response	Stable disease
	Target nodes/nodal masses, extranodal lesions	Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment.	< 50% decrease from baseline in SPD 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: • LDi > 1.5 cm AND • Increase by ≥ 50% from PPD nadir AND

Appendix 4
The Modified Lugano Classification: Revised Criteria for Response Assessment (cont.)

Response	Site	PET-CT–Based Response	CT-Based Response
			• An increase in LDi or SDi from nadir
		and/or	• 0.5 cm for lesions ≤ 2 cm
			• 1.0 cm for lesions > 2 cm
	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.
		and/or	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.
		and/or	Assessable disease of any size unequivocally attributable to lymphoma.
	Bone marrow	New or recurrent FDG-avid foci.	New or recurrent involvement

Appendix 4
The Modified Lugano Classification: Revised Criteria for Response Assessment (cont.)

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 5
A Bayesian Predictive Probability Design for Phase II Studies

The Phase II study is designed to test the null hypothesis H_0: $p \leq p_0$ at a level of α and to have sufficient power $1-\beta$ under the alternative hypothesis H_1: $p \geq p_1$, where p_0 is the response rate using standard treatment, p_1 is the target response rate of the study treatment, and α and β are the type I and type II error rates.

Bayesian framework starts with a prior $\pi(p) \sim$ Beta (a_0, b_0), a_0 and b_0 essentially indicating the number of prior responses and nonresponses.

The maximum number of patients is N_{max}. In the fixed sample design, the number of responses $X \sim$ Binomial (N_{max}, p) and the posterior distribution of the response rate is $P|X=x \sim$ Beta (a_0+x, $b_0+N_{max}-x$).

H_0 is rejected if the posterior probability $\Pr(P>p_0|X=x) > \theta_T$, where θ_T is the threshold for the posterior probability that would be used to reject the null hypothesis at the end of the study.

At an interim analysis the number of patients is $n \leq N_{max}$, the number of responses $X \sim$ Binomial (n, p) and the posterior distribution of the response rate is $P|X=x \sim$ Beta (a_0+x, b_0+n-x). The distribution of the number of responses in the potential $m=N_{max}-n$ future patients is $Y \sim$ Beta-Binomial (m, a_0+x, b_0+n-x). For any given $Y=i$, the probability that the response rate is larger than p_0 given $x+i$ responses in $n+m=N_{max}$ patients is $B_i=\Pr(P>p_0|X=x, Y=i)$. The predictive probability (PP) of concluding a positive result at the end of the study based on the current data is given by the weighted sum.

$$PP = \sum_{i=0}^{m} \Pr(Y=i|X=x) \times I\{\Pr(P_E - P_C > \delta | X=x, Y=i) > \theta_T\},$$

where the posterior probability in the index function is numerically solved in R, since the distribution of the response rate difference, i.e., the difference of two beta random variables (posterior P_E of and posterior of P_C) are not analytically available.

Appendix 6
BCL-2 and c-MYC Immunohistochemistry Scoring Algorithm

Table 1 Criteria for VENTANA BCL-2 Diagnostic Assessment

Clinical Diagnosis	Clinical Score	Staining Criteria
Negative	0	No staining in tumor cells or $<50\%$ tumor cells with cytoplasmic BCL-2 staining of any intensity
	1+	$\geq 50\%$ of tumor cells with weak or higher cytoplasmic BCL-2 staining but $<50\%$ of tumor cells with moderate or strong staining intensity
Positive	2+	$\geq 50\%$ of tumor cells with moderate or higher cytoplasmic BCL-2 staining but $<50\%$ of tumor cells with strong staining intensity
	3+	$\geq 50\%$ of tumor cells with strong cytoplasmic BCL-2 staining

Table 2 Criteria for VENTANA c-MYC (Y69) Diagnostic Assessment

Clinical Diagnosis	Staining Criteria
Negative	$<40\%$ of target cells positive for c-MYC at any intensity above background staining. A positive cell is a target cell with staining in the majority of the nucleus.
Positive	$\geq 40\%$ of target cells positive for c-MYC at any intensity above background staining. A positive cell is a target cell with staining in the majority of the nucleus.