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

**NCT Number:** NCT03135262

**Document Date:** Protocol Version 4: 13-June-2018

# PROTOCOL

| | |
|---|---|
| **TITLE:** | **A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH IDASANUTLIN AND VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA AND OBINUTUZUMAB OR RITUXIMAB IN COMBINATION WITH IDASANUTLIN AND VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA** |
| **PROTOCOL NUMBER:** | BH39147 |
| **VERSION NUMBER:** | 4 |
| **EUDRACT NUMBER:** | 2016-002480-34 |
| **IND NUMBER:** | 127311 |
| **TEST PRODUCTS:** | Obinutuzumab (RO5072759)<br>Rituximab (RO0452294)<br>Idasanutlin (RO5503781)<br>Venetoclax (RO5537382) |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.D. |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **DATE FINAL:** | Version 2: 17 January 2017 |
| **DATES AMENDED:** | Version 3: 1 March 2017<br>Version 4: See electronic date stamp below. |

| **Approver's Name** | **Title** | **Date and Time (UTC)** |
|---|---|---|
| [redacted] | Company Signatory | 13-Jun-2018 07:09:19 |

## PROTOCOL AMENDMENT, VERSION 4:
## RATIONALE OF CHANGES FROM VERSION 3 TO 4

Changes to Protocol BH39147, along with a rationale for each change, are summarized below.

- The option to delay, suspend, or terminate enrollment within a given arm has been added to the protocol (Section 3.1.1) to allow flexibility in trial management, balancing safety and efficacy, due to the nature of the Phase Ib/II study.
- Granulocyte colony-stimulating factor (G-CSF) use is now allowed in Cycles 1 and 2 (dose-limiting toxicity [DLT] observation window) to treat Grade $\geq 3$ neutropenia in the dose-escalation phase to optimize benefit/risk. The definition for DLT has been updated accordingly in Sections 3.1.2.1 and 4.4.1. Table 17 has been also updated to align guidelines for G-CSF use.
- The option to open the bridging cohorts upon Sponsor decision based on clinical judgment has been added to the protocol (Section 3.1.2.2) to allow flexibility in trial management, balancing safety and efficacy, due to the nature of the Phase Ib/II study.
- The option to collect visible manifestation or lymphoma involvement or toxicities has been added (Section 4.5.3) to allow collection of such data upon additional consent.
- Footnote "gg" related to positron emission tomography (PET)-computed tomography (CT) at end of induction in Appendix 2 was referenced by mistake. A new footnote "oo" has been added.
- New safety language regarding collection of special situation cases has been included in the protocol as a corrective measure to address a self-identified process gap related to the collection of overdose, medication errors, drug abuse, and drug misuse from interventional clinical trials (Sections 4.3.2, 5.4, and 5.4.4).
- The duration of male contraception period in Sections 4.1.1, 5.1.4.5, and 5.4.3.2 has been corrected from 6 months to 3 months based on requirements for each treatment drug (no requirement for venetoclax, 3 months each for idasanutlin, obinutuzumab, and rituximab).
- The duration of female contraception period in Sections 4.1.1 and 5.4.3.1 has been clarified based on requirements for each treatment drug (obinutuzumab vs. rituximab). In addition, text has been added to Section 4.1.1 to specify when women must refrain from donating eggs.
- Instructions about patient withdrawal from the Research Biosample Repository (RBR) after site closure have been modified to indicate that the investigator must inform the Sponsor of patient withdrawal by emailing the study number and patient number to global_rcr-withdrawal@roche.com (see Section 4.5.9.6).

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

## TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

## LIST OF APPENDICES

## PROTOCOL AMENDMENT ACCEPTANCE FORM

| | |
|---|---|
| **TITLE:** | **A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH IDASANUTLIN AND VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA AND OBINUTUZUMAB OR RITUXIMAB IN COMBINATION WITH IDASANUTLIN AND VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA** |
| **PROTOCOL NUMBER:** | BH39147 |
| **VERSION NUMBER:** | 4 |
| **EUDRACT NUMBER:** | 2016-002480-34 |
| **IND NUMBER:** | 127311 |
| **TEST PRODUCTS:** | Obinutuzumab (RO5072759)<br>Rituximab (RO0452294)<br>Idasanutlin (RO5503781)<br>Venetoclax (RO5537382) |
| **MEDICAL MONITOR:** | [redacted], M.D., Ph.D. |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH IDASANUTLIN AND VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA AND OBINUTUZUMAB OR RITUXIMAB IN COMBINATION WITH IDASANUTLIN AND VENETOCLAX IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA** |
| **PROTOCOL NUMBER:** | BH39147 |
| **VERSION NUMBER:** | 4 |
| **EUDRACT NUMBER:** | 2016-002480-34 |
| **IND NUMBER:** | 127311 |
| **TEST PRODUCTS:** | Obinutuzumab (RO5072759)<br>Rituximab (RO0452294)<br>Idasanutlin (RO5503781)<br>Venetoclax (RO5537382) |
| **PHASE:** | Phase Ib/II |
| **INDICATION:** | Relapsed or refractory follicular lymphoma or diffuse large B-cell lymphoma |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**Objectives and Endpoints**

This study will evaluate the safety, efficacy, and pharmacokinetics (PK) of obinutuzumab in combination with idasanutlin and venetoclax in patients with relapsed or refractory (R/R) follicular lymphoma (FL) and rituximab in combination idasanutlin and venetoclax in patients with R/R diffuse large B-cell lymphoma (DLBCL), with safety being the primary objective for the dose-escalation phase and the expansion phase of the study and efficacy being the primary objective for the expansion phase. PK objectives are secondary and exploratory. Specific objectives and corresponding endpoints for the study are outlined below.

**Safety Objective**

The safety objectives for this study are as follows:

- To determine the recommended Phase II doses (RP2Ds) for idasanutlin and venetoclax when given in combination with a fixed dose of obinutuzumab or rituximab during the dose-escalation phase on the basis of the following endpoint:
  - Incidence of dose-limiting toxicities (DLTs) during the first two cycles of study treatment
- To evaluate the safety and tolerability of obinutuzumab or rituximab in combination with idasanutlin and venetoclax, during dose-escalation and expansion phases, on the basis of the following endpoints:
  - Nature, frequency, severity, and timing of adverse events, including DLTs

- Changes in vital signs, ECGs, and clinical laboratory results during and following study treatment administration

**Efficacy Objectives**

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

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of obinutuzumab in combination with idasanutlin and venetoclax in R/R FL and rituximab in combination with idasanutlin and venetoclax in R/R DLBCL on the basis of the following endpoint:

- Complete response (CR) at the end of induction (EOI), as determined by the IRC on the basis of PET-CT scans

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of obinutuzumab in combination with idasanutlin and venetoclax in R/R FL and rituximab in combination with idasanutlin and venetoclax in R/R DLBCL on the basis of the following endpoints within each disease cohort:

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

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of obinutuzumab or rituximab in combination with idasanutlin and venetoclax on the basis of the following endpoints:

- For patients who have positive PET scans at the EOI:
  - CR at 12 months, as determined by the IRC and by the investigator on the basis of PET-CT scans, in patients with FL
  - CR at end of consolidation (EOC), as determined by the IRC and by the investigator on the basis of PET-CT scans, in patients with DLBCL
- Progression-free survival, defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by the investigator on the basis of CT scans alone, or death from any cause
- Event-free survival, defined as the time from initiation of study treatment to any treatment failure, including disease progression or relapse, as determined by the investigator on the basis of CT scans alone, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first
- Disease-free survival, defined, among patients achieving a CR, as the time from the first occurrence of a documented CR to relapse, as determined by the investigator on the basis of CT scans alone, or death from any cause, whichever occurs first
- Overall survival, defined as the time from initiation of study treatment to death from any cause

- Additional descriptive analysis based on TP53 status will be performed on the following endpoint:
  - CR at the EOI, as determined by the IRC on the basis of PET-CT scans

**Pharmacokinetic Objectives**

The PK objectives for this study are as follows:

Secondary PK Objectives

- To characterize the PK profiles of obinutuzumab or rituximab, idasanutlin (and its metabolites, if appropriate) and venetoclax to support dose escalation
- To assess potential PK interactions between idasanutlin, venetoclax, and obinutuzumab or rituximab

Exploratory PK Objective

- To explore PK exposure-effect (including pharmacodynamic, efficacy, and adverse event) relationships

**Biomarker Objective**

The exploratory biomarker objective for this study is to identify non-inherited biomarkers that are associated with response to study treatment (i.e., that could serve to inform precision healthcare approaches with predictive and/or prognostic potential), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity, can increase the knowledge and understanding of lymphoma biology or study treatment mechanism of action, or can contribute to improvement of diagnostic assays, on the basis of the following

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

**Study Design**

**Description of Study**

This Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study will evaluate the safety, efficacy, and pharmacokinetics of obinutuzumab in combination with idasanutlin and venetoclax in patients with R/R FL and rituximab in combination with idasanutlin and venetoclax in patients with R/R DLBCL. The study will include an initial dose-escalation phase followed by an expansion phase. The dose-escalation phase is designed to determine the RP2Ds and regimen for idasanutlin and venetoclax in combination with obinutuzumab for FL patients and in combination with rituximab for DLBCL patients. Dose escalation starts with idasanutlin and venetoclax in combination with obinutuzumab in all patients (FL and DLBCL) until the MTD (Regimen A) *or until Sponsor decision based on clinical judgment*, followed by:

- Dose confirmation and potential dose escalation in patients with DLBCL for idasanutlin and venetoclax in combination with rituximab to determine the RP2Ds for this combination
- Dose confirmation and potential dose escalation in patients with FL with a different regimen (Regimen B, obinutuzumab given alone in Cycle 1 followed by idasanutlin, venetoclax, and obinutuzumab in combination in Cycles 2–6) to determine the RP2Ds for this regimen

The RP2Ds and regimen for FL and RP2Ds for DLBCL will be decided at the end of dose-escalation phase. Different RP2Ds and/or regimens may apply for FL and DLBCL, respectively.

In the expansion phase, patients with FL will receive idasanutlin and venetoclax at the RP2Ds of the selected regimen (Regimen A or B) in combination with obinutuzumab, and patients with DLBCL will receive idasanutlin and venetoclax at the RP2Ds in combination with rituximab.

Patients with R/R FL enrolled in the dose-escalation and expansion phases may be eligible to receive post-induction treatment (referred to as maintenance) with obinutuzumab, venetoclax, and idasanutlin.

Patients with R/R DLBCL enrolled in the dose-escalation and expansion phases may be eligible to receive post-induction treatment (referred to as consolidation) with obinutuzumab or rituximab, venetoclax, and idasanutlin. Patients who receive obinutuzumab during induction will continue to receive obinutuzumab in consolidation, and patients who receive rituximab during induction will continue to receive rituximab in consolidation.

**Number of Patients**

Approximately 140 patients with R/R FL and DLBCL are expected to be enrolled in this study at approximately 25 investigational sites worldwide.

**Target Population**

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ages ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- B-cell lymphoma classified as either of the following:
  - R/R FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody
  - Relapsed or refractory DLBCL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody in patients who are not eligible for second-line combination chemotherapy and autologous stem-cell transplantation, have failed second-line combination chemotherapy, or experienced disease progression following autologous stem-cell transplantation
- Histologically documented CD20-positive lymphoma, as determined by a local laboratory
- Fluorodeoxyglucose-avid lymphoma (i.e., PET-positive lymphoma)
- At least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension by CT scan or magnetic resonance imaging)
- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL
  - If the archival tissue is unavailable or unacceptable, a pretreatment core-needle, excisional or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable.
  - If a patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, a core-needle biopsy is strongly recommended.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) *or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:*
  - *Women must remain abstinent* or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 18 months after the last dose of study treatment *for those treated with obinutuzumab, idasanutlin, and venetoclax; and for at least 12 months after the last dose of study treatment for those treated with rituximab, idasanutlin, and venetoclax. Women must refrain from donating eggs during this same period.*
  - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
  - With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least $3$ months after the last dose of study treatment. Men must refrain from donating sperm during this same period.
  - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study treatment to avoid exposing the embryo.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

- Known CD20-negative status at relapse or progression
- Prior allogeneic SCT
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1
- Prior standard or investigational anti-cancer therapy as specified below:
  - Radioimmunoconjugate within 12 weeks prior to Day 1 of Cycle 1
  - Monoclonal antibody or antibody–drug conjugate therapy within 4 weeks prior to Day 1 of Cycle 1
  - Radiotherapy, chemotherapy, hormonal therapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1
- Clinically significant toxicity (other than alopecia) from prior therapy that has not resolved to Grade $\leq 2$ (according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE v4.0]) prior to Day 1 of Cycle 1
- Grade 3b FL
- History of transformation of indolent disease to DLBCL (expansion-phase only)
  - History of transformation of indolent disease is allowed in the dose escalation phase.
- Central nervous system lymphoma or leptomeningeal infiltration
- Treatment with systemic corticosteroids $> 20$ mg/day, prednisone or equivalent
  - Patients receiving corticosteroids $\leq 20$ mg/day, prednisone or equivalent, must be documented to be on a stable dose for at least 4 weeks prior to Day 1 of Cycle 1.
  - If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, 100 mg of prednisone or equivalent can be given for a maximum of 5 days, but all tumor assessments must be completed prior to start of corticosteroid treatment.

- Clinical conditions requiring treatment with oral or parenteral anticoagulants or antiplatelet agents (e.g., chronic daily treatment with aspirin $>$ 325 mg/day, clopidogrel, warfarin, systemic low-molecular-weight heparin) unless treatment can be discontinued 7 days (or 5 half-lives) prior to initiation of study treatment (except used as flushes for indwelling catheters)
- Refusal of blood products and/or sensitivity to blood products
- History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies
- Known hypersensitivity or allergy to murine products or any component of the obinutuzumab, rituximab, idasanutlin, or venetoclax formulation
- Infection considered by the investigator to be clinically uncontrolled or poses an unacceptable risk to the patient upon the induction of neutropenia, that is, patients who are or should be on antimicrobial agents for the treatment of active infection such as the following:
  - Fungal infection with visceral involvement, other than mucosal candidiasis, with $<$ 2 weeks of appropriate systemic antifungal therapy
  - Bacterial infection with positive cultures within 7 days prior to initiation of study treatment
  - Patients who have received $<$ 5 days of appropriate therapeutic antibiotic therapy for an identified infection
  - Neutropenic fever considered infection related within 72 hours prior to initiation of study treatment
  - History of symptomatic C. difficile infection that required treatment within 1 month prior to dosing

    Upon clinical response to *C. difficile* treatment, the stool consistency and frequency must have returned to normal.

  In all cases, the patient should be afebrile and hemodynamically stable for at least 72 hours at the time of study treatment initiation.
- Caution should be exercised when considering the use of obinutuzumab or rituximab in patients with a history of recurring or chronic infections.
- Treatment with the following agents within 7 days prior to the first dose of venetoclax and idasanutlin:
  - Strong and moderate CYP3A inhibitors such as fluconazole, ketoconazole, and clarithromycin
  - Moderate CYP3A inducers such as bosetan
  - CYP2C8 substrates such as repaglinide
  - UGT1A3 inhibitors such as gemfibrozil
  - OATP1B1/3 substrates such as statin drugs
- Treatment with the following agents within 14 days prior to the first dose of venetoclax and idasanutlin:
  - Strong CYP3A inducers such as rifampin (also a CYP2C8 inducer) and carbamazepine
- Chronic use of CYP2C8 or OATP1B1/3 substrates
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade that contains 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 (e.g., Child-Pugh class B and C)

- Current or history of hepatitis B virus or hepatitis C virus (HCV) infection: positive for hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), or HCV antibody at screening
  - Patients are eligible if both HBsAg and HBcAb are negative but tested positive for hepatitis B surface antibody after vaccination.
- Known history of HIV-positive status
  - For patients with unknown HIV status, HIV testing must be performed at screening if not in contradiction with local regulations.
- History of progressive multifocal leukoencephalopathy
- Vaccination with a live virus vaccine within 28 days prior to Day 1 of Cycle 1
- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:
  - Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer
  - Any previously treated malignancy that has been in remission without treatment for $\geq 2$ years prior to enrollment
- Evidence of any significant, uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm), or uncontrolled irritable bowel disease (i.e., Crohn disease, ulcerative colitis, diverticulosis-associated colitis, and Behçet disease)
- Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by study treatment, such as severe hereditary coagulation disorders or insulin-dependent diabetes mellitus that is not optimally controlled with medical management (e.g., presence of ketoacidosis)
- Major surgical procedure other than for diagnosis within 28 days prior to Day 1 of Cycle 1, or anticipation of a major surgical procedure during the study
- Inadequate hematologic function (unless due to underlying lymphoma), defined as follows:
  - Hemoglobin $< 9$ g/dL
  - ANC $< 1.5 \times 10^9$ cells/L
  - Platelet count $< 75 \times 10^9$ cells/L
- Any of the following abnormal laboratory values (unless due to underlying lymphoma):
  - Calculated creatinine clearance $< 50$ mL/min using the modified Cockcroft-Gault
  - Patients with clinically significant persistent electrolyte abnormalities, such as hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypermagnesemia of Grade $> 1$ according to NCI CTCAE, v4.0
  - Treatment for correction of above electrolyte imbalances is permitted during screening to meet eligibility criteria.
  - AST or ALT $> 2.5 \times$ upper limit of normal (ULN)
  - Serum total bilirubin $> 1.5 \times$ ULN (or $> 3 \times$ ULN for patients with Gilbert syndrome)
  - INR or PT $> 1.5 \times$ ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT $> 1.5 \times$ ULN in the absence of a lupus anticoagulant
- Pregnancy or lactation, or plans to become pregnant during the study
- Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to Day 1 of Cycle 1.

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

**End of Study**

The end of this study is defined as the time when both of the following conditions are met:

- All enrolled patients with FL have completed or discontinued study treatment (including induction and maintenance, as applicable), and
- All enrolled patients with DLBCL have been followed for at least 1 year after they have completed or discontinued study treatment (including induction and consolidation, as applicable).

**Length of Study**

The total length of the study is expected to be approximately 48 months.

## Investigational Medicinal Products

**Test Product (Investigational Drug)**

Study treatment will be administered in 28-day cycles.

Obinutuzumab will be administered by intravenous infusion at an absolute (flat) dose of 1000 mg on Days 1, 8, and 15 of the first cycle and on Day 1 of each subsequent cycle during induction treatment, and on Day 1 of every other month (i.e., every 2 months) for 24 months during maintenance treatment (eligible patients with FL only) or for 6 months during consolidation treatment (eligible patients with DLBCL only).

Rituximab will be administered by intravenous infusion at a dose of 375 mg/m$^2$ on Day 1 of Cycles 1–6 during induction treatment and on Day 1 of every other month (i.e., every 2 months) for 6 months during consolidation treatment (eligible patients with DLBCL only).

Idasanutlin tablets will be taken once daily by mouth, approximately 15 minutes after eating a meal and with water, on Days 1–5 of Cycles 1–6 (or Cycles 2–6 for the bridging cohorts in FL patients and in the expansion phase if this regimen is chosen), followed by 6 months of post-induction treatment. The starting dose will be 100 mg during the dose-escalation phase. The RP2D with the selected regimen will be administered during the expansion phase. The dose and regimen for post-induction treatment will be determined by the Sponsor after review of all relevant data.

Each once-daily dose of venetoclax will be taken orally with approximately 240 mL of water within approximately 30 minutes after the completion of breakfast or the first meal of the day. For Cycles 1–6 (induction; or Cycles 2–6 for the bridging cohorts in FL patients and in the expansion phase if this regimen is chosen) and for 6 months thereafter (post-induction), venetoclax will be given once-daily on Days 1–5 or Days 1–10 depending on tolerability. The selection of the venetoclax dose schedule will be determined according to the dose-escalation plan. The starting dose will be 200 mg during the dose-escalation phase. The RP2D with the selected regimen will be administered during the expansion phase. The dose and regimen for post-induction treatment will be determined by the Sponsor after review of all relevant data.

## Statistical Methods

**Primary Analysis**

Safety

The safety analysis population will include all patients who have received at least one dose of any component of the combination, whether patients are prematurely withdrawn from the study or not. All safety parameters will be summarized and presented in tables based on this safety population.

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

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

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

Efficacy

The primary efficacy analysis will include all patients enrolled in the expansion phase who receive at least one dose of any component of the combination. Data from patients who were dosed at the RP2D and selected regimen during the dose-escalation phase may be pooled with the corresponding arm of the expansion phase, depending on their indication.

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

**Determination of Sample Size**

The primary efficacy analysis for the expansion phase will be estimation of the true proportion of patients expected to obtain a PET-defined CR at EOI. A sample size of 40 patients is deemed sufficient to provide adequate precision for the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting probability of response of $<$40% in FL, and 40% in DLBCL assuming an observed PET-defined CR rate of 55%.

**Interim Analyses**

During the expansion phase, predictive probabilities may be used to guide early stopping for futility by comparing the observed proportion of patients who achieve a PET-CT–defined CR at the EOI with that in historical controls. The design is based on Lee and Liu (2008), with the modification that the uncertainty in historical control data is fully taken into account by utilizing a distribution on the control response rate. Interim analysis decision rules will be based on the predictive probability that this trial will have a positive outcome if carried out to completion and will use the historical control data available at the time of analysis.

It is anticipated that at least one interim analysis per disease indication will be conducted during the expansion phase of the study, with the earliest interim analysis taking place when at least 15 patients treated have been evaluated for a PET-CT–defined CR at EOI. If, at any interim analysis, a low predictive probability suggests that the proportion of patients achieving a PET-CT–defined CR at EOI is lower than desired, the IMC will review the data and decide whether to recommend an early decision to stop enrollment.

Additional review of safety and/or efficacy data by the IMC may be requested by and carried out at the discretion of the Medical Monitor. Further details regarding the rules and guidelines of data will be provided in an IMC charter.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ABC | activated B cell–like (subgroup) |
| ADCC | antibody-dependent cellular cytotoxicity |
| ADCP | antibody-dependent cellular phagocytosis |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| aPTT | activated partial thromboplastin time |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| AUC | area under the concentration–time curve |
| BID | twice daily |
| BR | bendamustine and rituximab |
| BSA | body surface area |
| CDC | complement-dependent cytotoxicity |
| CI | confidence interval |
| CHOP | cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone |
| CLL | chronic lymphocytic leukemia |
| $C_{max}$ | maximum serum concentration |
| CML | chronic myelogenous leukemia |
| CR | complete response |
| CRi | complete remission with incomplete blood count recovery |
| CRp | complete remission with incomplete platelet count recovery |
| CSR | Clinical Study Report |
| CT | computed tomography |
| CVP | cyclophosphamide, vincristine, and prednisone |
| CYP | cytochrome P450 |
| DDI | drug–drug interaction |
| DFS | disease-free survival |
| DLBCL | diffuse large B-cell lymphoma |
| DLT | dose-limiting toxicity |
| EC | Ethics Committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |

| Abbreviation | Definition |
|---|---|
| EFS | event-free survival |
| EOC | end of consolidation |
| EOI | end of induction |
| EORTC | European Organization for Research and Treatment of Cancer |
| ESMO | European Society for Medical Oncology |
| FCBL | fold change from baseline |
| FDA | (U.S.) Food and Drug Administration |
| FDG | fluorodeoxyglucose |
| FFPE | formalin-fixed, paraffin-embedded |
| FL | follicular lymphoma |
| FLIPI, FLIPI2 | Follicular Lymphoma International Prognostic Index, Follicular Lymphoma International Prognostic Index 2 |
| G | obinutuzumab (GA101) |
| GB | obinutuzumab plus bendamustine |
| GCB | germinal-center B cell–like (subgroup) |
| G-CHOP | obinutuzumab plus CHOP |
| GCP | Good Clinical Practice |
| G-CSF | granulocyte colony-stimulating factor |
| GI | gastrointestinal |
| HBcAb | hepatitis B core antibody |
| HBsAb | hepatitis B surface antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HI | hematologic improvement |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | hazard ratio |
| ICH | International Council for Harmonisation |
| Ig | immunoglobulin |
| IHC | immunohistochemistry |
| IMC | internal monitoring committee |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (Application) |
| IPI | International Prognostic Index |
| IRB | Institutional Review Board |
| IRC | Independent Review Committee |

| Abbreviation | Definition |
|---|---|
| IRR | infusion-related reaction |
| IV | intravenous |
| IxRS | interactive voice or Web-based response system |
| JC | John Cunningham (virus) |
| LMWH | low-molecular-weight heparin |
| MBP | microprecipitated bulk |
| MCL | mantle-cell lymphoma |
| mCRM | modified Continual Reassessment Model |
| MDM2 | murine double minute 2 |
| MIC-1 | macrophage inhibitory cytokine−1 |
| MLFS | morphologic leukemia-free state |
| MRD | minimal residual disease |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| MUGA | multigated acquisition (scan) |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NHL | non-Hodgkin's lymphoma |
| NK | natural killer |
| OATP | organic anion-transporting polypeptide |
| ORR | objective response rate |
| OS | overall survival |
| PBMC | peripheral blood mononuclear cell |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PK | pharmacokinetic |
| PML | progressive multifocal leukoencephalopathy |
| PO | orally (by mouth) |
| PR | partial response |
| QD | once a day |
| QTcF | QT interval corrected using Fridericia's formula |
| RBR | Research Biosample Repository |
| R-CHOP | rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone |
| RP2D | recommended Phase II dose |
| R/R | relapsed or refractory |
| SCID | severely compromised immunodeficient |

| Abbreviation | Definition |
|---|---|
| SCT | stem-cell transplantation |
| SD | stable disease |
| SDP | spray-dried powder |
| SLL | small lymphocytic lymphoma |
| SOC | System Organ Class |
| SPD | sum of the product of the diameters |
| TGI | tumor growth inhibition |
| TLS | tumor lysis syndrome |
| ULN | upper limit of normal |
| WM | Waldenström's macroglobulinemia |

# 1. BACKGROUND

## 1.1 BACKGROUND ON NON-HODGKIN'S LYMPHOMA

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

### 1.1.1 Follicular Lymphoma

Indolent B-cell lymphomas are a heterogeneous group of malignant lymphomas and account for approximately one-third of all NHLs. Follicular lymphoma (FL) is the most common subtype of indolent B-cell lymphoma, accounting for about 22% of all newly diagnosed cases of NHL (Armitage and Weisenburger 1998). Approximately 90% of the cases have a t(14;18) translocation, which juxtaposes *BCL2* with the IgH locus and results in overexpression of the anti-apoptotic protein, Bcl-2.

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

Despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, most patients will eventually experience disease relapse. Relapses are characterized by increasing refractoriness and decreasing duration of response to subsequent lines of therapy. Thus, new treatments are needed to improve the outcome for these patients.

### 1.1.2 Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive NHL, accounting for approximately 30% of all NHLs diagnosed annually (Armitage and Weisenburger 1998). The use of immunochemotherapy, most commonly R-CHOP (rituximab plus CHOP), for newly diagnosed DLBCL led to a significant improvement in survival in patients of all age groups. In older patients (>60 years), R-CHOP was associated with a 2-year event-free survival (EFS) rate of 57% and a 10-year survival rate of 43.5% (Coiffier et al. 2010). In younger patients (18–60 years old) with favorable prognostic features, R-CHOP demonstrated a 3-year EFS rate of 79% and a survival

rate at 3 and 6 years of 93% and 74.3%, respectively (Pfreundschuh et al. 2011). However, nearly 40% of patients with DLBCL will eventually die of relapsed disease or disease that is refractory to first-line treatment. Patients with a high-risk International Prognostic Index (IPI) have a 5-year PFS rate of 40% following treatment with R-CHOP (Zhou et al. 2014).

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

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

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

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

## 1.2 BACKGROUND ON OBINUTUZUMAB

Obinutuzumab (also known as GA101) is a novel glycoengineered type II anti-CD20 antibody. Compared with rituximab, obinutuzumab is characterized by more potent direct B-cell death induction and increased affinity for FcγRIII receptors expressed on natural killer (NK) cells, macrophages, and monocytes, resulting in enhanced antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) (Beers et al. 2010; Mössner et al. 2010; Herter et al. 2014). Together, these characteristics confer obinutuzumab with enhanced immune effector functions and B cell–depleting activity compared with rituximab.

Obinutuzumab is approved for the treatment of patients with relapsed or refractory (R/R) FL and is approved for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). Obinutuzumab is also approved for use in combination with bendamustine followed by obinutuzumab maintenance for the treatment of patients with FL who did not respond to or who progressed during or after treatment with rituximab or a rituximab-containing regimen. Obinutuzumab continues to be investigated in a large clinical program.

Background on rituximab can be found in Sections 1.1 and 1.5.

### 1.2.1 Nonclinical Studies with Obinutuzumab

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

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

### 1.2.2 Clinical Studies with Obinutuzumab

As of 4 July 2016, clinical data from Roche-sponsored studies on obinutuzumab are available from 13 clinical studies: 8 Phase I or II studies (BO20999, BO21003, JO21900, BO21000, GAO4915g, GAO4779g, YP25623, and GAO4768g) and 5 Phase III/IIIb studies (BO21004/CLL11, GAO4753g, MO28543, BO21223, and BO21005). Available efficacy results from the NHL cohorts in these studies and available safety results from all patients are summarized below. Efficacy data from a Phase III study (GAO4753g) of obinutuzumab are also presented. Studies BO21223 (in previously untreated patients with indolent NHL) and BO21005 (in previously untreated patients with DLBCL) have passed futility analyses on efficacy, are ongoing, and remain blinded.

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

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

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

In early studies of obinutuzumab in combination with chemotherapy (e.g., CHOP or bendamustine) in patients with previously untreated or R/R NHL (Studies BO21000, GAO4915g, and GAO4753g), the proportion of patients with a CR or PR at the end of induction (EOI) treatment ranged from 69% to 96%. The CR rate was higher with combination therapy (35%–39% in patients with previously untreated FL, 39%–50% in patients with R/R FL, and 55% in patients with previously untreated DLBCL) than with monotherapy (see Obinutuzumab Investigator's Brochure).

A Phase III study, GAO4753g, investigated obinutuzumab plus bendamustine (GB) compared with bendamustine alone in patients with R/R indolent NHL ($n = 396$). Patients in the GB group who had not experienced disease progression at the EOI received obinutuzumab monotherapy every 2 months for up to 2 years. PFS was significantly longer in the GB arm, with a median PFS of 29 versus 14 months (hazard ratio [HR]: 0.48; 95% CI: 0.35, 0.67; $p < 0.0001$) (Sehn 2015; Trněný et al. 2016). Obinutuzumab was granted approval for use in patients with FL who did not respond to or who progressed during or after treatment with rituximab or a rituximab-containing regimen (see Section 1.2).

A Phase III study, BO21223, investigated obinutuzumab plus chemotherapy (G-benda, G-CVP, obinutuzumab plus CHOP [G-CHOP]) compared with rituximab plus chemotherapy followed by obinutuzumab or rituximab maintenance in patients with previously untreated indolent NHL (FL cohort, $n = 1202$). On the basis of positive results that demonstrated significant improvement in PFS in the obinutuzumab plus chemotherapy arm, the independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor at a pre-planned interim analysis.

A Phase III study, BO21005, investigated G-CHOP compared with R-CHOP in patients with previously untreated DLBCL. The study did not meet its primary endpoint of PFS difference at final analysis. Based upon the BO21005 efficacy results, this study protocol has been amended (Version 3) to cease evaluating obinutuzumab in patients with R/R DLBCL in the expansion phase. Patients with DLBCL enrolled after the identification of idasanutlin and venetoclax maximum tolerated dose (MTD) in

combination with obinutuzumab will instead receive idasanutlin and venetoclax in combination with rituximab.

#### 1.2.2.2 Clinical Safety of Obinutuzumab

As of 4 July 2016, an estimated 4454 patients with NHL (including DLBCL, indolent B-cell lymphoma, and CLL) have been treated with obinutuzumab given as monotherapy or in combination with CHOP, bendamustine, fludarabine plus cyclophosphamide, or chlorambucil, at doses ranging from 50 mg to 2000 mg. Overall, the safety of obinutuzumab monotherapy and obinutuzumab combination therapy was manageable.

The most frequent causes of death were disease progression and adverse events associated with infectious diseases. This is consistent with the study population and the disease under treatment. The incidence of fatal adverse events was similar across all ongoing trials. In Study GAO4768g (obinutuzumab 1000 mg vs. 2000 mg), the incidence of deaths did not increase with increased obinutuzumab dose (7.5% and 2.6%, respectively).

Of particular interest, a high incidence of infusion-related reactions (IRRs) was observed consistently in all obinutuzumab trials. The reported incidence of IRRs varied across studies. In the CLL population, the incidence ranged from 66% in previously untreated patients receiving obinutuzumab plus chlorambucil (Study BO21004) to 100% in patients with R/R disease receiving obinutuzumab monotherapy (pooled data from Studies BO21003 and BO20999).

In the NHL population, the incidence of IRRs in studies of obinutuzumab monotherapy was 75.1% (pooled data from Study BO21003 and from the high-dose NHL cohorts from Study BO20999). In studies of obinutuzumab in combination with either CHOP (Study GAO4915g) or bendamustine (Study BO21000), the incidence of IRRs, regardless of the relationship with obinutuzumab, was 70%–78%. IRRs mainly occurred during Cycle 1, with a higher frequency reported on the first day of treatment.

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

#### 1.2.2.3 Clinical Pharmacokinetics of Obinutuzumab

On the basis of available pharmacokinetic (PK) data, a two-compartment PK model comprising both a linear clearance pathway and a nonlinear time-varying clearance pathway adequately describes serum obinutuzumab concentration data. The initial

clearance of obinutuzumab is approximately 2.8 times higher than the steady-state clearance, consistent with a decrease in the time-varying clearance component, which is high at the start of treatment and declines with repeated cycles of obinutuzumab treatment. The time-varying clearance pathway is consistent with target-mediated drug disposition, such that at the start of treatment, there is a large quantity of CD20-positive cells that rapidly bind to obinutuzumab. Repeated dosing of obinutuzumab saturates the pool of CD20-positive cells, hence reducing clearance via this pathway. The linear clearance pathway is consistent with catabolism of immunoglobulin (Ig) G antibodies and is therefore independent of CD20-positive cells. Refer to the Obinutuzumab Investigator's Brochure for additional details.

## 1.3 BACKGROUND ON IDASANUTLIN

The tumor suppressor p53 plays a pivotal role in protection from cancer development. p53 is a transcription factor that is activated following stress and regulates multiple downstream genes implicated in cell-cycle control, apoptosis, DNA repair, and senescence in non-stressed cells (Ray-Coquard et al. 2012); the level of p53 is controlled tightly by murine double minute 2 (MDM2). MDM2 regulates p53 through a negative feedback loop, and when the nuclear p53 level is elevated, it activates transcription of the *MDM2* gene. In turn, MDM2 binds to p53 and blocks its transactivation domain. MDM2 also serves as a p53 ubiquitin ligase that targets p53 for ubiquitin-dependent degradation in the proteasome. Both p53 and MDM2 have a short half-life and their nuclear concentrations are kept very low as a result of the functioning of the regulatory circuit. However, in cancer cells overexpressing MDM2, this feedback loop is dysregulated. Stress-induced p53 activation mechanisms in these tumors are believed to be inadequate, leading to inefficient growth arrest and/or apoptosis.

Therefore, blocking the p53–MDM2 interaction is expected to overcome the oncogenic consequences of MDM2 overproduction, leading to enhanced p53 stabilization and function (Ray-Coquard et al. 2012). Treatment of cancer cells expressing functional p53 with MDM2 antagonists should result in the concurrent transcriptional activation of p53 downstream genes, cell-cycle arrest, and apoptosis.

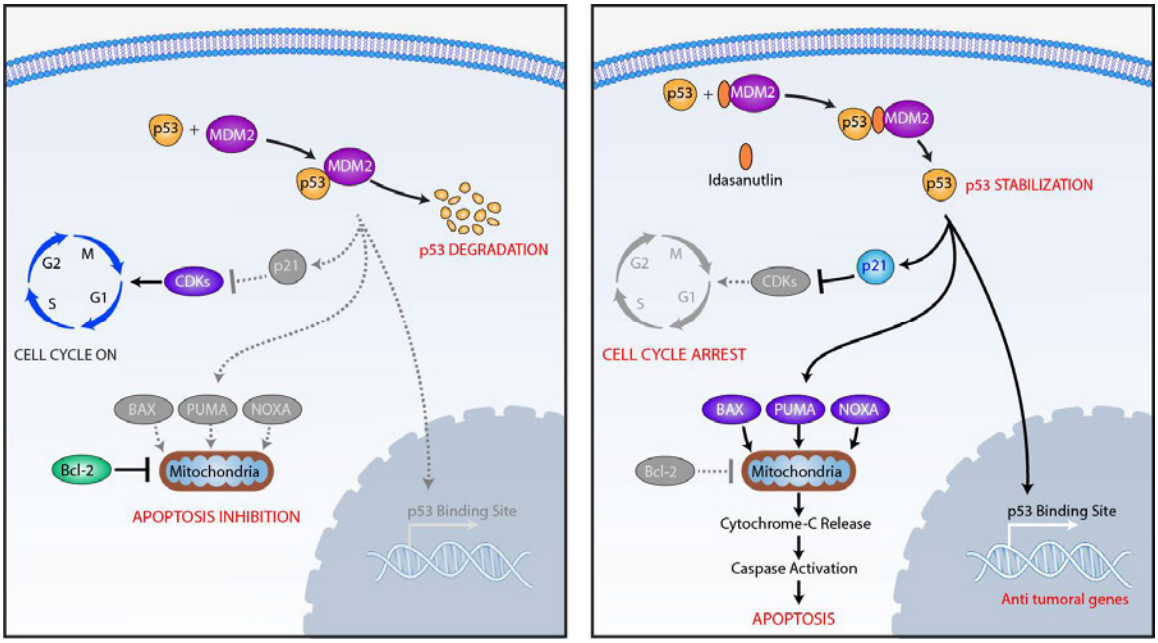
A class of imidazoline compounds was identified as potent and selective inhibitors of the p53–MDM2 interaction (Vassilev et al. 2004). These molecules, part of the family of nutlins, interact specifically with the p53-binding pocket of MDM2 and, thus, free p53 from negative feedback mechanisms. Treatment of cancer cells with nutlins activates the p53 pathway leading to activation of *P53* target genes, cell-cycle arrest, apoptosis, and/or senescence (Tovar et al. 2006; Vassilev et al. 2007).

The imadazoline RO5045337 was the first member of the nutlin family of MDM2 antagonists tested in humans and is the predecessor of the pyrrolidine idasanutlin (RO5503781), the compound that will be investigated in this study. Both compounds bind selectively to the p53 binding site on the surface of the MDM2 molecule in vitro with high affinity. The compound has good oral bioavailability and has shown tumor growth

inhibition (TGI) in four mouse xenograft models of human cancer, including two NHL models tested at doses that did not cause noteworthy toxicity.

In cell-free assays, idasanutlin has been shown to bind to the MDM2 protein with high affinity ($K_d = 5.7$ nM) and to inhibit MDM2–p53 binding with an $IC_{50}$ of $6.6 \pm 1.0$ nM. Exposure of tumor cells, including lymphoma cells to the compound, leads to a dose-dependent accumulation of p53 protein and activation of its transcriptional targets and the p53 pathway. As a result, cancer cells undergo a cell-cycle block during G1 and G2 phases followed by apoptosis in vitro and in vivo (see Figure 1) (Ding et al. 2013).

**Figure 1 Regulation of p53 Stability and Activity by MDM2**




BAX = BCL-2–associated X protein; BCL-2 = B-cell lymphoma 2 protein; CDKs = cyclin-dependent kinases; Cyto C = cytochrome C; G1 = Growth 1/Gap 1 phase; G2 = Growth 2/Gap 2 phase; M = mitosis; MDM2 = murine double minute 2; NOXA = phorbol-12-myristate-13-acetate–induced protein 1, p21 = cyclin-dependent kinase inhibitor 1A (CDKN1A, CIP1); PUMA = p53 upregulated modulator of apoptosis; S = synthesis phase.

### 1.3.1 Quality Development

Two oral compounds of the drug family of nutlins binding to an identical binding site have been investigated in clinical studies: RO5045337, the predecessor molecule with lower affinity was evaluated in 350 patients in total, and an improved selective MDM2 inhibitor with increased target affinity and pharmacokinetic properties, idasanutlin, which is used in all ongoing and planned studies. Tablets manufactured with the amorphous compound were originally developed with a microprecipitated bulk powder (MBP) formulation and used to treat 209 patients in early clinical studies. Using an alternative

approach to stabilize the amorphous state of the drug substance, a spray-dried powder (SDP) formulation was developed. PK results from a relative bioavailability study (NP28902, Part 2) demonstrated that the SDP formulation has an increased maximum concentration ($C_{max}$) observed and exposure (area under the concentration–time curve [AUC]) compared with the MBP formulation and similar patient variability in exposure.

Based on these positive results, as well as the reduced formation of a genotoxic impurity, the SDP formulation is planned for use in all future clinical development. Subsequently, an optimized SDP formulation (filler and film-coat color change) has been developed for use in the proposed Phase Ib/II study. Similar systemic exposures, safety, and efficacy can be achieved with a reduced dose of the SDP formulation (300 mg twice daily [BID]) compared with the MBP formulation (600 mg BID). As of 13 September 2016, 357 patients have been treated with idasanutlin (both formulations: 191 patients with acute myeloid leukemia (AML) and 166 patients with solid tumors or NHL.

### 1.3.2 Clinical Studies with RO5045337 and Idasanutlin

Initial proof of mechanism for MDM2 inhibition leading to p53 activation was demonstrated in solid tumors with RO50405337; however, the best response observed in patients with relapsed solid tumors was stable disease (SD) (RO5045337 Investigator's Brochure).

In the RO5045337 leukemia study (NO21279), 96 patients whose disease was R/R to available standard-of-care regimens were treated in Stratum A (AML, acute lymphocytic leukemia [ALL], and chronic myelogenous leukemia [CML]) and 20 patients in Stratum B (CLL) during dose escalation. The doses ranged from 20 mg/m$^2$ to 1920 mg/m$^2$. One patient achieved a PR (and continued to receive 25 cycles; the patient had a history of Richter syndrome), and 15 patients showed SD with this early formulation of the MDM2 inhibitor.

Six patients experienced at least one Grade 4 adverse event. Grade 4 adverse events in patients with CLL included pneumonia, hypophosphatemia, febrile neutropenia, and hemorrhagic stroke (reported in 1 patient each), and anemia and thrombocytopenia (in 2 patients each). The events were considered by the investigator to be study treatment related. Patients received treatment for the adverse event and continued study treatment without dose adjustments. No dose-limiting toxicities (DLTs) were reported in the 20 patients with CLL.

As of 13 September 2016, idasanutlin had been studied in 298 patients in the Phase I/Ib program, including 131 patients with AML (and 1 patient with CML), 160 patients in the solid tumor setting, and 6 patients with NHL.

The idasanutlin solid tumor study (NP27872; n = 99) tested different doses and schedules using the MBP formulation. The study was an entry-into-human, multiple-ascending dose-escalation study with two dosing schedules (weekly × 3 [Schedule A] vs.

daily [×5 or ×3; Schedule B], each administered on a 28-day cycle duration) escalating independently. Each schedule started with a single-patient dose escalation at a dose of 100 mg. The five most common tumor types were leiomyosarcoma (8 of 99 patients [8.1%]), liposarcoma (7 of 99 [7.1%]), and adenocarcinoma of the colon, rectal adenocarcinoma, and transitional cell carcinoma (5 of 99 patients [5.1%] each). The MTD for weekly dosing (Schedule A) was determined as 1600 mg BID, with DLTs of nausea (Grade 3), vomiting (Grade 3), and thrombocytopenia (Grade 4). For daily×5 dosing (Schedule B), the MTD was determined to be 500 mg once a day (QD), with DLTs of thrombocytopenia (Grade 4; including the preferred term "platelet count decreased"), neutropenia (Grade 4), febrile neutropenia (Grades 3 and 4), leukopenia (Grade 4), and diarrhea (Grade 3). For daily ×3 dosing (Schedule B), the MTD was determined to be 500 mg BID, with DLTs of pancytopenia (Grade 4), thrombocytopenia (Grades 3 and 4), febrile neutropenia (Grade 3), and neutropenia (Grade 4) reported. Eight of 34 patients treated QD×5 days had a best response of SD.

Three patients with NHL were treated in this study (2 patients at 500 mg BID×3 days and 1 patient at 400 mg BID×5 days with the MBP formulation), and no differences in safety profile of patients with lymphoma compared with that of patients with solid tumors could be detected. One patient with anaplastic lymphoma had a Grade 3 adverse event of neutropenic sepsis (reported as being unrelated to study drug) and prolonged Grade 4 thrombocytopenia for 55 days (related to study drug). One patient with DLBCL had a Grade 3 serious adverse event of febrile neutropenia and Grade 4 thrombocytopenia (both related to study drug) and discontinued treatment.

One patient with DLBCL also had GI toxicity presenting as Grade 3 diarrhea and Grade 3 nausea, as well as hematologic toxicity in terms of concurrent Grade 4 thrombocytopenia, Grade 4 neutropenia, and Grade 3 anemia, which were all mitigated by blood transfusions and growth factors.

In the Phase I/Ib AML study, NP28679, 46 patients were treated with monotherapy and 76 patients were treated with combination therapy with cytarabine.

As of the clinical cutoff date (15 April 2016), of the 17 (of 20) response-evaluable patients treated with idasanutlin monotherapy during the dose-escalation period in Part 1, the best hematologic malignancy responses during treatment were as follows:
2 patients achieved a CR (1 patient had received no prior cancer therapies and continued to have a CR for >1 year from initiation of therapy, and the other patient had prior therapy for myelofibrosis and was relapse free for >9 months), 3 patients achieved complete remission with incomplete blood count recovery (CRi)/morphologic leukemia-free state (MLFS), 3 patients achieved a PR, and 4 patients experienced hematologic improvement (HI). HI was defined as decreased percentage of peripheral blasts, decreased frequency of transfusions, and improvement in peripheral cell counts (Martinelli et al. 2016).

Eight of 9 patients were evaluable for response in the Part 1 extension. Response assessments indicated 2 patients each with CR/CRp or CRi/MLFS (1 patient bridged to an allogeneic transplant and 1 patient discontinued on Day 737), and 2 patients with HI.

In the Part 2 (idasanutlin plus cytarabine) dose escalation in 22 response-evaluable patients, there were 6 patients with a best response of CR/CRp, 1 with CRi/MLFS, and 2 patients each with a PR and HI. In the Part 2 extension phase of the study, 17 patients received idasanutlin monotherapy and 21 patients received combination therapy with cytarabine. More patients treated with idasanutlin plus cytarabine achieved CR/CRp than those treated with idasanutlin alone in the Part 2 extension phase. A total of 5 of 16 response-evaluable patients achieved a CR/CRp following treatment with idasanutlin plus cytarabine; all 5 patients had a CR, with 1 patient bridged to transplant prior to confirmation but remained as having a CR following transplant. Only 1 of the 17 response-evaluable patients in the Part 2 extension treated with idasanutlin alone had a CR/CRp.

Initial analysis of the number of prior regimens for antecedent hematologic disease or antecedent malignancy, number of prior therapies for AML, exposure, and best response in the study for patients treated with idasanutlin in combination with cytarabine (Part 2, Part 2 extension, and Part 4) demonstrated activity in patients who received prior cytarabine-containing regimens and had R/R disease. One patient with AML treated with idasanutlin plus cytarabine in Study NP28679 achieved a CR despite harboring a *TP53* mutation.

In Part 4 of the study, 10 of 31 response-evaluable patients who were treated with the SDP formulation of idasanutlin in combination with cytarabine achieved a CR/CRp (9 CRs and 1 CRp) and 3 patients achieved a CRi/MLFS (1 CRi and 2 MLFS) (cutoff, 15 April 2016; enrollment is complete).

In a Phase Ib/II study, GH29914, 10 patients have received combination therapy with venetoclax and the SDP formulation of idasanutlin until the cutoff date of 13 September 2016. Three dosing cohorts have been evaluated to date: 3 patients received 400 mg/200 mg (venetoclax/idasanutlin), 3 patients received 400 mg/400 mg, and 4 patients received 600 mg/200 mg.

In a Phase Ib/II NHL study, BH29812, 6 patients were treated with two different idasanutlin dose levels as of 13 September 2016. Three patients each were treated with 100 mg of idasanutlin plus 1000 mg of obinutuzumab or 150 mg of idasanutlin plus 1000 mg of obinutuzumab, respectively. All 6 patients cleared the DLT period and 5 were safely treated in Cycle 2. One patient discontinued after Cycle 1 due to disease progression.

#### 1.3.2.1 Clinical Pharmacology

### Clinical Pharmacokinetics

Clinical pharmacokinetics obtained from studies in patients with solid tumors (Studies NP27872 and NP28902) or AML (Study NP28679) treated with idasanutlin at daily doses ranging from 100 to 3200 mg or weekly doses of 400 or 800 mg are summarized as follows:

- Half-life was approximately 1 day; the half-life was the same on the weekly schedule as on Day 3 or Day 5 of the daily schedules.
- For AUC values, intrapatient variability was $<30\%$ and interpatient variability was approximately 50%.
- East-Asian ethnicity, age, sex, and concomitant cytarabine treatment did not have an apparent effect on PK exposure.
- The SDP formulation was tested in Studies NP28679 and NP28902 and appears to be twice more bioavailable than the MBP formulation.
- No major effect of low-fat and high-fat meals was observed on pharmacokinetics of the SDP formulation to be used in the current study.
- Idasanutlin is 99.99% protein bound; bone marrow exposure is approximately 70% of its plasma level at steady state. Idasanutlin and its metabolites are mainly excreted via the hepatic route through bile, with minimal ($<1\%$) renal elimination.

### Clinical Pharmacodynamics

Serum levels of macrophage inhibitory cytokine−1 (MIC-1), a secreted protein that is transcriptionally induced by p53 (with the promotor containing two p53 response elements), have been used to assess pharmacodynamic (PD) effects in all clinical studies. Following a single dose, an increase in MIC-1 levels by fold change from baseline (FCBL) was observed. Such correlations between MDM2-antagonist therapeutic level exposure and MIC-1 increase, as measured by FCBL, was identified in early studies of RO5045337 in liposarcoma (Ray-Coquard et al. 2012) and have been further validated as a biomarker tracking with therapeutic exposure of the current MDM2-antagonist idasanutlin in AML.

No correlation was apparent between idasanutlin plasma concentration and QT interval corrected using Fridericia's formula (QTcF).

### Drug-Drug Interactions

Idasanutlin is a cytochrome P450 (CYP) 2C8 inhibitor that could affect concomitant CYP2C8 substrates at therapeutic exposure levels. Its M4 metabolite is an organic anion-transporting polypeptide (OATP)-1B1/3 transporter inhibitor that has been shown to inhibit OATP1B1 and OATP1B3 in vitro, and thus concomitant use of OATP1B1 and OATP1B3 substrates, including statins, is to be avoided. These are the basis for the prohibited therapy list for idasanutlin in this study (see Section 4.4.2). However, idasanutlin is not expected to interact with substrates of deaminases such as cytarabine (no interaction observed with cytarabine in Study NP28679). Analysis of this potential

interaction will continue in the ongoing Phase I/Ib study NP28679 in AML, which is expected to be completed in December of 2016.

Only one metabolite, RO6802287 (M4) (~25% of parent exposure), which is inactive, was identified. This metabolite was generated by CYP3A4 and CYP2C8 at an approximate 50:50 ratio. A strong CYP3A4 inhibitor, posaconazole, had no effect on idasanutlin $C_{max}$ but increased AUC values by 32%, which suggests a minimal (not clinically significant) drug–drug interaction (DDI) potential with use of a single strong or moderate CYP3A4 or CYP2C8 inhibitor (assuming the same minimal effect, as the two isozymes have the metabolic pathway for idasanutlin). UGT1A3 may be a major clearing enzyme for idasanutlin; its strong inhibitor gemfibrozil will be excluded from use in the current study.

As idasanutlin is a substrate for both CYP3A4 and CYP2C8, the known strong and moderate inducers of CYP3A4 or CYP2C8 (only one, i.e., rifampicin, which is also a CYP3A4 inducer) will only be allowed after washing out with sufficient duration during the post-DLT window to prevent potential loss of exposure for idasanutlin and/or venetoclax. The known inducers of CYP3A4 will be prohibited during the first 2 cycles of induction, and guidance is provided for their use in the remainder of the study (Section 4.4.2, Table 10).

See the Idasanutlin Investigator's Brochure for additional details on nonclinical and clinical studies.

#### 1.3.2.2 Clinical Safety of Idasanutlin

**Solid Tumors: Studies NP27872 and NP28902**

A total of 160 patients with advanced malignancies (excluding leukemia) received idasanutlin in Study NP27872 (study now completed; cutoff date for safety data, 2 September 2014; 99 patients) and Study NP28902 (study now completed; data cutoff date, 5 May 2015; 61 patients). All 99 patients in Study NP27872 experienced at least one adverse event, with diarrhea, nausea, vomiting, decreased appetite, and thrombocytopenia being the most common adverse events. Grade $\geq 3$ adverse events were reported for 63.6% of patients with solid tumors treated with idasanutlin in Study NP27872, most commonly from the Blood and Lymphatic System Disorders, GI Disorders, and Metabolism and Nutritional Disorders System Organ Classes (SOCs).

In Study NP28902, 85%–100% of patients in each cohort experienced at least one adverse event. The most common adverse events were diarrhea, nausea, decreased platelet count, vomiting, fatigue, constipation, and decreased appetite. GI events were the most common study drug–related adverse events across all treatment groups and occurred during the days of treatment. The events were reversible and manageable with anti-emetic and antidiarrheal treatments for subsequent cycles.

Serious adverse events were reported for 32 of 99 patients in Study NP27872, most commonly thrombocytopenia, febrile neutropenia, neutropenia, anemia, and leukopenia, and for 16 of 61 patients in Study NP28902, most commonly pyrexia, cellulitis, and dehydration. Overall, seven deaths in Study NP27872 and three deaths in Study NP28902 were reported. Of the seven deaths reported in Study NP27872, five were attributed to disease progression, one was attributed to intra-abdominal hemorrhage with pulmonary embolism (unrelated), and one was due to pulmonary embolism (Phase I category: remotely related). In Study NP28902, the cause of death for 2 patients was attributed to disease progression and pneumonia aspiration, which was considered by the investigator to be unrelated to study drug.

### Acute Myeloid Leukemia: Studies NP28679 and GH29914

Overall, the current safety profile of Study NP28679 is consistent with findings from other studies in patients with R/R AML treated with cytarabine.

As of 15 April 2016, all patients in NP28679 (n = 122) had experienced at least one adverse event. The most common adverse events across the study groups were from the GI Disorders SOC; in particular, patients experienced diarrhea and nausea, and to a lesser extent, vomiting. These events were also the most common adverse events considered by investigators to be related to study treatment. Serious adverse events occurred in 71 of 122 patients during the study; the most common were infectious and hematologic events. Infectious adverse events were more common for patients with AML compared with patients with solid tumors (Studies NP27872 and NP28902). Of the 25 of the 71 serious adverse events that were considered by investigators to be related to study treatment, the most frequent events were sepsis and febrile neutropenia.

Overall, there were 27 deaths reported during the study, 16 of which were associated with or resulted from adverse events. Of the eight deaths considered by investigators to be related to study treatment, the causes of death were identified as sepsis (3 patients), pneumonia (1 patient), *Clostridium difficile* infection (1 patient), *Scedosporium* infection (1 patient), neutropenic colitis (1 patient), and neutropenic sepsis (1 patient).

Although the MTD was not reached in a formal manner for the 56 patients with AML during dose escalation, the clinical experience for patients treated at 800 mg BID was evaluated by investigators as not tolerable for those patients, primarily due to GI adverse events (mainly diarrhea) and bone marrow failure (DLT), and further dose escalations were not recommended. Although there are fewer patients treated with the SDP formulation than with the MBP formulation across all studies (solid tumor and AML), there do not appear to be differences in tolerability and/or collective safety parameters.

The adverse event profile of the SDP formulation of idasanutlin with cutoff date of 25 February 2015 (Part 4) is similar to that of the MBP (see Appendix 13).

In a Phase Ib/II study (GH29914) in elderly patients with R/R AML, 10 patients have received combination therapy with venetoclax (daily dosing) and idasanutlin (Days 1–5) till the cutoff date of 13 September 2016. Three dosing cohorts have been evaluated to date: 3 patients received 400 mg/200 mg (venetoclax/idasanutlin), 3 patients received 400 mg/400 mg, and 4 patients received 600 mg/200 mg. Of the 10 patients enrolled, 9 patients developed at least one adverse event. Similar to other idasanutlin trials, the most common adverse events were reported from SOC infection and infestations and SOC GI disorders across all study groups. There were no fatal adverse events. One case of a serious Grade 3 DLT of asthenia was reported in the 600 mg/200 mg group and was considered related to study treatment by the investigator.

## 1.4 BACKGROUND ON VENETOCLAX

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

### 1.4.1 Nonclinical Studies with Venetoclax

In vitro, venetoclax demonstrated broad cell-killing activity against a panel of lymphoma and leukemia cells, including B-cell FL, mantle-cell lymphoma (MCL), DLBCL, and AML. Venetoclax was especially potent against cell lines that expressed high levels of Bcl-2. Leukemia and lymphoma cell lines that bore the t(14;18) translocation were significantly more sensitive to venetoclax than wild-type cell lines.

Venetoclax inhibited subcutaneous murine xenograft growth of human tumor cell lines derived from ALL and NHL.

The PK profile of venetoclax was evaluated in multiple animal species. In mice, rats, monkeys, and dogs, low plasma clearance and low volumes of distribution characterized the venetoclax PK profile. Half-lives ranged from 2.2 hours in monkeys to 12 hours in dogs. Food had a marked effect on the oral bioavailability in dogs.

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

A more detailed discussion of the nonclinical activity of venetoclax, including pharmacokinetic, toxicology, and metabolism, is provided in the current Venetoclax Investigator's Brochure.

### 1.4.2 Clinical Studies with Venetoclax

As of 28 November 2015, on the basis of data available in the AbbVie and Genentech/Roche clinical databases, a total of 1662 patients have been exposed to at least one dose of venetoclax in the oncology and immunology development programs. A total of 1498 oncology patients had data available in AbbVie and Genentech/Roche studies as of 28 November 2015. Of the 1498 patients, 935 patients had CLL/small lymphocytic leukemia (SLL), 346 patients had NHL, 115 patients had MM, and 102 had AML. An additional 66 participants were healthy volunteers. A total of 564 oncology patients received the drug as monotherapy, 933 received the drug in combination with other therapies, and 1 patient received venetoclax as a single dose in a DDI study and did not re-enroll in a subsequent monotherapy study. Additionally, 98 patients had been exposed to at least one dose of venetoclax in the AbbVie immunology study, M13-093, as of 28 November 2015.

Three ongoing Phase Ib/II studies, GP28331, GO28440, and GO27878, include the combination of obinutuzumab and venetoclax in CLL and NHL, respectively. In addition, Study BO25323, a Phase III randomized study evaluating the efficacy of obinutuzumab plus venetoclax compared with obinutuzumab plus chlorambucil in patients with previously untreated CLL, is ongoing.

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

#### 1.4.2.1 Clinical Results in Non-Hodgkin's Lymphoma

Study M12-175, the first-in-human venetoclax monotherapy dose-escalation study, is ongoing in patients with R/R CLL/SLL and NHL. Two DLTs have been reported in patients with NHL who were treated with venetoclax in Study M12-175. Both DLTs occurred at the 600-mg dose in Cohort 5 (which enrolled a total of 10 patients and had a 300-mg lead-in dose and 600-mg designated-cohort dose). One patient experienced a DLT of serious Grade 3 febrile neutropenia, and the other patient experienced a DLT of non-serious Grade 4 neutropenia. Dosing was interrupted, and patients were treated with medication; the events resolved and patients restarted therapy at a reduced venetoclax dose of 300 mg. No DLTs were reported in Cohorts 6–8, with the maximum dose of 1200 mg studied.

The most common adverse events in the NHL cohort of Study M12-175 were nausea, anemia, diarrhea, and fatigue, all occurring in $\geq$20% of patients. Grade $\geq$3 hematologic toxicity was less common in patients with NHL than in patients with CLL. In Study

M12-175, 13% of patients with NHL experienced Grade ≥3 neutropenia and 10% experienced Grade ≥3 thrombocytopenia.

As of 15 September 2015, a total of 106 patients were enrolled in the R/R NHL arm of Study M12-175 (70 patients in the dose-escalation cohorts and 36 in the safety-expansion cohort) and evaluated for objective response following the International Working Group criteria (patients with Waldenstrom's macroglobulinemia [WM] were evaluated using the International Workshop [IW]-WM criteria). The investigator-assessed objective response rate (ORR) for all FL patients and DLBCL patients (across dose-escalation and safety-expansion cohorts), excluding DLBCL-Richter's transformation patients, was 37.9% and 17.6%, respectively; a CR was achieved by 4 patients in each group (13.8% and 11.8%, respectively).

Study M12-630 is evaluating venetoclax in combination with bendamustine and rituximab (BR) in patients with R/R NHL. Patients receive this regimen for six cycles. In Study M12-630, preliminary efficacy data are available for 48 patients with R/R NHL as of 17 September 2015. Median time on study was 5.3 months (range: 0.1 to 38.1 months). The ORR was 67.4% (31 of 48 evaluable patients), with a CR in 13 patients (28.3%) and a PR in 18 patients (39.1%). An additional 3 patients (6.5%) had SD. Hematologic toxicity in this study was not significantly greater than that expected with BR alone.

Study GO27878 is a Phase Ib/II study evaluating venetoclax in combination with either obinutuzumab plus CHOP (G-CHOP) or R-CHOP in patients with NHL. Patients received CHOP for six cycles, obinutuzumab or rituximab for eight cycles, and venetoclax for eight cycles (Days 4–10 in Cycle 1 and Days 1–10 in subsequent cycles). The recommended dose of venetoclax was found to be 800 mg in the R-CHOP arm and has yet to be identified in the G-CHOP arm, as dosing continues beyond 800 mg. Venetoclax in combination with either R-CHOP or G-CHOP was well tolerated, and response rates were very promising (Zelenetz et al. 2016).

Additional details on the clinical activity and safety of venetoclax are provided in the Venetoclax Investigator's Brochure.

#### 1.4.2.2 Clinical Pharmacokinetics and Pharmacodynamics

Venetoclax clinical pharmacology has been evaluated in several Phase I to III clinical trials, and preliminary data are available in the Investigator's Brochure.

The venetoclax formulation being used in clinical trials is a tablet formulation in strengths of 10, 50, and 100 mg. After a single dose in patients with CLL/SLL, after a low-fat meal, venetoclax plasma concentrations peaked at approximately 6 hours after dosing. The mean harmonic terminal phase elimination half-life ($t_{1/2}$) of venetoclax was approximately 17 hours, and the mean oral clearance was approximately 13 L/hour. No accumulation was seen after repeated QD administration of venetoclax over the 100 to 800 mg QD

dose range in patients with CLL/SLL. Preliminary data from patients with CLL/SLL suggested that venetoclax AUC was approximately dose-proportional across the 150- to 1200-mg dose levels at steady state. Preliminary data did not suggest apparent PK differences among patients with CLL/SLL, NHL, MM, or AML. Low-fat and high-fat meals increased the exposure compared with fasting in healthy volunteers by approximately 3.4- and 5.1-fold, respectively. Venetoclax should always be given after a low-fat meal.

Venetoclax is eliminated almost entirely through the hepatic route via metabolism by the CYP3A enzyme system. Specific recommendations are provided for co-administration of venetoclax with moderate and strong inhibitors and inducers of CYP3A. Venetoclax does not appear to be a clinically significant inhibitor of CYP2C9.

Preliminary results from a dose- and exposure-response analysis based on Study M12-175 data indicate that there is no relationship between venetoclax dose or exposure and QT interval corrected using QTcF for doses up to 1200 mg (8 μg/mL plasma concentrations) of venetoclax.

Venetoclax and its M27 metabolite are predominantly metabolized by cytochrome P450 (CYP) 3A4 (CYP3A4) in vitro; UDP-glucuronosyltransferases (UGTs) are not involved in the metabolism of venetoclax. Venetoclax is also substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters. No active uptake of venetoclax was observed in cells overexpressing organic anion transporting polypeptide 1B1 (OATP1B1) or OATP1B3. Based on in vitro results, venetoclax is a P-gp, BCRP, and OATP1B1 inhibitor. It is not a potent in vitro inhibitor of CYP3A4, CYP1A2, CYP2B6, or CYP2D6 ($IC_{50}$ > 30 μM); and it does not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM. Venetoclax is also not predicted to cause inhibition of CYP2C19, CYP2C8, CYP2C9, or UGT1A1 at clinically relevant concentrations. It is not an inhibitor of UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

Refer to the Venetoclax Investigator's Brochure for additional details on nonclinical and clinical studies.

There is no clinically relevant DDI expected among the three combined drugs in the present study.

## 1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

FL remains an incurable disease with the currently available therapies (see Section 1.1.1). Despite significant therapeutic progress with the use of immunochemotherapy as first-line treatment, most patients will eventually experience disease relapse. Relapses are characterized by increasing refractoriness and decreasing duration of response to subsequent lines of therapy. Thus, new treatments are needed to improve the outcome for patients.

DLBCL is the most common aggressive NHL (see Section 1.1.2), accounting for approximately 30% of all NHLs diagnosed annually. Despite significant therapeutic progress with the addition of rituximab to chemotherapy in the first-line treatment of patients with B-cell NHL, FL and DLBCL remain an area of high medical need in which novel targeted therapies are required to improve patient outcome (see Section 1.1).

Obinutuzumab is a humanized glycoengineered type II anti-CD20 monoclonal antibody with high-affinity binding to the CD20 antigen; high ADCC and ADCP; low complement-dependent cytotoxicity (CDC) activity; and high direct cell death induction. Rituximab is a chimeric murine/human monoclonal antibody that binds to CD20 and eliminates CD20-expressing B cells via a number of different mechanisms, including ADCC, CDC, and apoptosis.

Although monotherapy studies with obinutuzumab or rituximab show good response, the limited CR rates indicate the potential need for a combination with a cytotoxic therapy, or at least one other targeted drug with independent but complementary mechanisms of action.

In a RO5045337 AML/CLL study (NO21279), 20 patients with CLL were treated with the suboptimal version and formulation of the MDM2 inhibitor. The dose ranged from 20 mg/m$^2$ to 1920 mg/m$^2$. In total, 15 patients had SD and 1 patient with Richter syndrome achieved a PR and continued to receive 25 cycles. MDM2 inhibitor single-dose therapy is safe but does not lead to relevant clinical responses in CLL, in spite of PD biomarker activity. The idasanutlin MBP formulation was tested in a solid tumor study in 95 patients at different doses and schedules, which led to different MTDs that were dependent on dose and schedule. Three patients with NHL tolerated the treatment well, but one DLT occurred as prolonged thrombocytopenia. No differences were observed in the safety profile for patients treated with 400 and 500 mg on Days 1–5 BID (MBP formulation).

Venetoclax is a specific inhibitor of the Bcl-2 anti-apoptotic protein expressed in many NHL cells. Bcl-2 is overexpressed in most FL and many DLBCLs as a consequence of the t(14;18) chromosomal translocation or gene amplification and is associated with a poor prognosis in multiple tumor types (Cory and Adams 2002; Cory et al. 2003; Reed 2008; Iqbal et al. 2011). Bcl-2 has been shown to contribute to resistance of malignant cells to chemotherapies with varied mechanisms of action, consistent with its role as an inhibitor of the final common steps of apoptosis, and is likely to play a role in resistance to the pro-apoptotic activities of immunotherapy and chemotherapy. In solid and hematologic tumor models, antimitotic drugs (taxanes and auristatin) were shown to modulate Bcl-2 prosurvival proteins to induce cell death in vitro (Haldar et al. 1998; Poruchynsky et al. 1998; Wertz et al. 2011).

MDM2 and Bcl-2 are important players in major common molecular pathways with regard to the control of cell survival or apoptosis induction. Inhibition of both proteins is

likely to create a synergy of action at a cellular level, leading to a more efficient induction of cell death (Oren 2003; Harris and Levine 2005; Mahfoudhi et al. 2016; Valente et al. 2016). Moreover, idasanutlin may be able to downregulate Mcl-1 through inhibition of MDM2, a known resistance factor for venetoclax. Therefore, the addition of venetoclax, a Bcl-2 inhibitor, to an MDM2 inhibitor may have the potential to significantly enhance the anti-lymphoma activity and to result in improved clinical outcomes.

Nonclinical data that support the triplet combination of obinutuzumab or rituximab with idasanutlin and venetoclax include the following:

- A DOHH-2 model in CB17 severely compromised immunodeficient (SCID) mice that demonstrated significantly improved anti-tumor activity of the triplet combination over the activity of any treatment regimen alone or doublet combination (obinutuzumab plus venetoclax or obinutuzumab plus idasanutlin; see Figure 7)
- A Z-138 model in CB17 SCID mice that demonstrated significantly improved anti-tumor activity of the triplet combination over the activity of any treatment regimen alone or doublet combination (obinutuzumab plus venetoclax or obinutuzumab plus idasanutlin; see Figure 10)
- A WSU-DLCL2 model in CB17 SCID mice that demonstrated significantly improved anti-tumor activity of the combination rituximab plus venetoclax (see Figure 9)

No nonclinical data with the combination of rituximab, idasanutlin, and venetoclax are available. Based on the results from the combination of obinutuzumab, idasanutlin, and venetoclax and their complementary mechanisms of action (direct cell death mediated by the anti-CD20 antibody and apoptosis mediated by idasanutlin and venetoclax), it is expected that rituximab in combination with idasanutlin and venetoclax would show superior anti-tumor activity compared with the single or doublet combination.

Although there is potential of overlapping toxicity with regard to bone marrow suppression (anemia, neutropenia, and thrombocytopenia) between obinutuzumab or rituximab, idasanutlin, and venetoclax, the Grade $\geq$3 adverse event rates of hematologic toxicities for obinutuzumab or rituximab are relatively low and range from 3% to 14% and 1% to 4%, respectively. These overlapping toxicities are readily manageable with growth factors, clinical monitoring, and supportive blood transfusions. Clear guidance on dose reduction and dose delays is in place, despite the low starting dose for idasanutlin and venetoclax, to mitigate potential overlapping toxicities.

In summary, Study BH39147 has been designed to explore different doses of idasanutlin and venetoclax in combination with a fixed dose of obinutuzumab or rituximab in patients with R/R FL and DLBCL, with the primary objective to determine the MTDs and recommended Phase II doses (RP2Ds) in combination with obinutuzumab or rituximab during the dose-escalation phase and the response rates in addition to safety, pharmacokinetics, and exploratory PD parameters in the expansion phase. The chemotherapy-free regimen being used seeks to offer more options for patients with R/R

NHL and could be the first step to future triple combinations free of conventional cytotoxic drugs.

Available nonclinical and clinical data suggest that there is a strong rationale to expect an improved benefit–risk profile with the triplet combination of obinutuzumab or rituximab, idasanutlin, and venetoclax. Furthermore, synergistic activity is expected to allow for efficacy at lower doses than single agents. This novel triplet regimen may have the potential to extend treatment-free remissions and decrease toxicity by improving on individual agents used as part of current standard of care. With the risk-minimization measures in place (see Section 5.1), the benefit–risk assessment is considered acceptable for the use of idasanutlin and venetoclax in combination with obinutuzumab or rituximab in this Phase Ib/II study.

This study will be conducted in parallel with the ongoing Phase Ib/II study BH29812, assessing the combination of obinutuzumab or rituximab and idasanutlin in a similar patient population. These two studies will be linked and will share information regarding the safety, tolerability, as well as the efficacy of the combination on a regular basis. As a safety measure, enrollment in Study BH39147 will start only after preliminary safety data from Study BH29812 become available. Dose escalation of idasanutlin in this study will occur after the same or a higher dose has been tested in Study BH29812. In addition, safety data from both Studies BH29812 and BH39147 will be integrated in a modified Continual Reassessment Model (mCRM) with overdose control (see Section 3.1.2.3) for selection of subsequent doses. Any safety signals, tolerability data, or efficacy data reported in one study will be assessed and immediately put in context with available data in the second study.

# 2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of obinutuzumab in combination with idasanutlin and venetoclax in patients with R/R FL and rituximab in combination idasanutlin and venetoclax in patients with R/R DLBCL, with safety being the primary objective in the dose-escalation phase and the expansion phase of the study and efficacy being the primary objective for the expansion phase. Specific objectives and corresponding endpoints for the study are outlined below.

In this study, “study treatment” refers to the protocol-mandated treatments under study (i.e., obinutuzumab, rituximab, idasanutlin, and venetoclax).

## 2.1 SAFETY OBJECTIVES

- To determine the RP2Ds for idasanutlin and venetoclax when given in combination with a fixed dose of obinutuzumab or rituximab during the dose-escalation phase on the basis of the following endpoint:
  - Incidence of DLTs during the first two cycles of study treatment

- To evaluate the safety and tolerability of obinutuzumab or rituximab in combination with idasanutlin and venetoclax during the dose-escalation and expansion phases on the basis of the following endpoints:
  - Nature, frequency, severity, and timing of adverse events, including DLTs
  - Changes in vital signs, ECGs, and clinical laboratory results during and following study treatment administration

## 2.2 EFFICACY OBJECTIVES

Response will be determined on the basis of positron emission tomography and computed tomography (PET-CT) scans or CT scans alone, using Revised Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014; see Appendix 4), hereinafter referred to as the modified Lugano 2014 criteria. Response will be determined by an independent review committee (IRC) and by the investigator.

### 2.2.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of obinutuzumab in combination with idasanutlin and venetoclax in R/R FL and rituximab in combination with idasanutlin and venetoclax in R/R DLBCL on the basis of the following endpoint:

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

### 2.2.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of obinutuzumab in combination with idasanutlin and venetoclax in R/R FL and rituximab in combination with idasanutlin and venetoclax in R/R DLBCL on the basis of the following endpoints within each disease cohort:

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

### 2.2.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of obinutuzumab or rituximab in combination with idasanutlin and venetoclax on the basis of the following endpoints:

- For patients who have positive PET scans at EOI:

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

  CR at end of consolidation (EOC), as determined by the IRC and by the investigator on the basis of PET-CT scans, in patients with DLBCL

- PFS, defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by the investigator on the basis of CT scans alone, or death from any cause
- EFS, defined as the time from initiation of study treatment to any treatment failure, including disease progression or relapse, as determined by the investigator on the basis of CT scans alone, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first
- Disease-free survival (DFS), defined, among patients achieving a CR, as the time from the first occurrence of a documented CR to relapse, as determined by the investigator on the basis of CT scans alone, or death from any cause, whichever occurs first
- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause
- Additional descriptive analysis based on TP53 status will be performed on the following endpoint:
  - CR at the EOI, as determined by the IRC on the basis of PET-CT scans

## 2.3 PHARMACOKINETIC OBJECTIVES

The PK objectives for this study are as follows:

**Secondary PK Objectives**

- To characterize the PK profiles of obinutuzumab or rituximab, idasanutlin (and its metabolites, if appropriate), and venetoclax to support dose escalation
- To assess potential PK interactions between idasanutlin, venetoclax, and obinutuzumab or rituximab

**Exploratory PK Objectives**

- To explore PK exposure-effect (including PD, efficacy, and adverse event) relationships

## 2.4 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify non-inherited biomarkers that are associated with response to study treatment (i.e., that could serve to inform precision healthcare approaches with predictive and/or prognostic potential), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events, can provide evidence of study treatment activity, can increase the knowledge and understanding of lymphoma biology or study treatment mechanism of action, or can contribute to improvement of diagnostic assays, on the basis of the following:

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

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF STUDY

### 3.1.1 Overview of Study

This Phase Ib/II, open-label, multicenter, non-randomized, dose-escalation study will evaluate the safety, efficacy, and pharmacokinetics of obinutuzumab in combination with idasanutlin and venetoclax in patients with R/R FL and rituximab in combination with idasanutlin and venetoclax in patients with R/R DLBCL. The study will include an initial dose-escalation phase followed by an expansion phase. The dose-escalation phase is designed to determine the RP2Ds and regimen for idasanutlin and venetoclax in combination with obinutuzumab for FL patients and in combination with rituximab for DLBCL patients. Dose escalation starts with idasanutlin and venetoclax in combination with obinutuzumab in all patients (FL and DLBCL) until the MTD (Regimen A) *or until Sponsor decision based on clinical judgment* (see Section 3.1.2), followed by:

- Dose confirmation and potential dose escalation in patients with DLBCL for idasanutlin and venetoclax in combination with rituximab to determine the RP2Ds for this combination
- Dose confirmation and potential dose escalation in patients with FL with a different regimen (Regimen B, obinutuzumab given alone in Cycle 1 followed by idasanutlin, venetoclax, and obinutuzumab in combination in Cycles 2–6) to determine the RP2Ds for this regimen

The RP2Ds and regimen for FL and RP2Ds for DLBCL will be decided at the end of dose-escalation phase. Different RP2Ds and/or regimens may apply for FL and DLBCL, respectively.

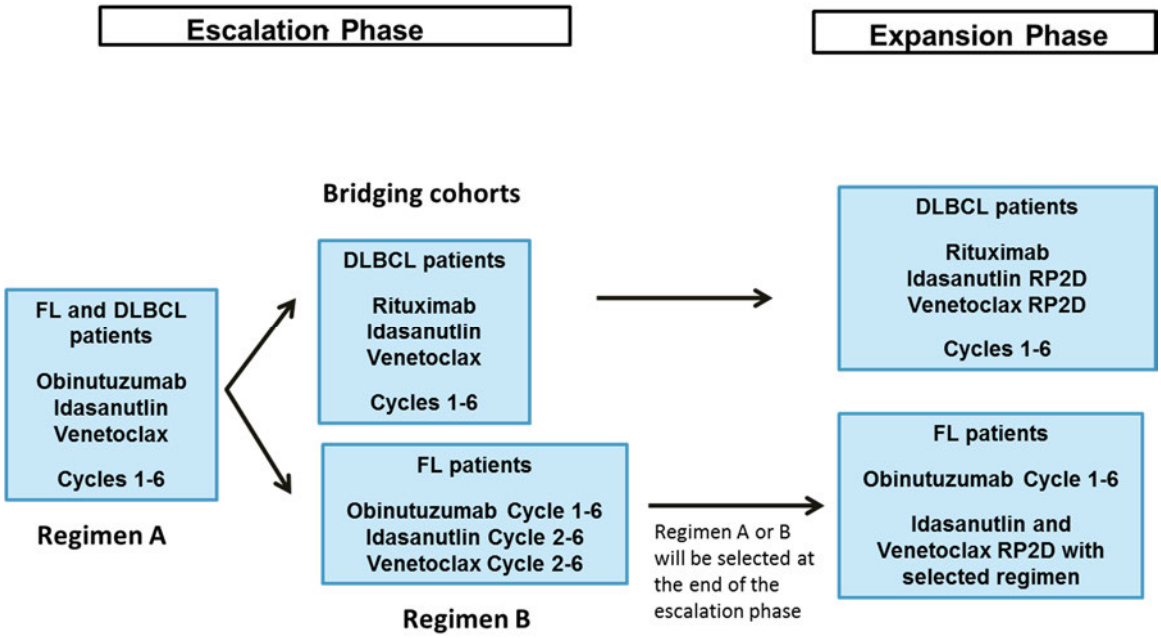
In the expansion phase, patients with FL will receive idasanutlin and venetoclax at the RP2Ds of the selected regimen (Regimen A or B) in combination with obinutuzumab, and patients with DLBCL will receive idasanutlin and venetoclax at the RP2Ds in combination with rituximab (see Section 3.1.3).

Patients with R/R FL enrolled in the dose-escalation and expansion phases may be eligible to receive post-induction treatment (referred to as maintenance) with obinutuzumab, venetoclax, and idasanutlin (see Sections 3.1.2.2 and 3.1.3, respectively, for details on the treatment regimens).

Patients with R/R DLBCL enrolled in the dose-escalation and expansion phases may be eligible to receive post-induction treatment (referred to as consolidation) with obinutuzumab or rituximab, venetoclax, and idasanutlin (see Section 3.1.2.2 for details on treatment regimens). Patients who receive obinutuzumab during induction will continue to receive obinutuzumab in consolidation, and patients who receive rituximab during induction will continue to receive rituximab in consolidation.

The study schema is presented in Figure 2.

**Figure 2 Study Schema**




DLBCL = diffuse large B-cell lymphoma; EOI = end of induction; FL = follicular lymphoma; RP2D = recommended Phase II dose.

Approximately 140 patients with R/R FL and DLBCL are expected to be enrolled in this study at approximately 25 investigational sites worldwide.

All patients will be closely monitored for adverse events throughout the study and for at least 90 days after the last dose of study treatment (see Section 5.3.1). Adverse events will be graded according to the National Cancer Institute Common Toxicity Criteria, Version 4.0 (NCI CTCAE v4.0). An internal monitoring committee (IMC) will be established to monitor patient safety throughout the study (see Section 3.1.4).

To characterize the PK properties of obinutuzumab or rituximab, idasanutlin, and venetoclax when given in combination, blood samples will be taken at various timepoints before and during study treatment administration (see Appendix 3).

Response will be determined by the IRC (see Section 3.1.5) and the investigator using the modified Lugano 2014 criteria (see Appendix 4). The primary efficacy endpoint will be based on IRC assessment of response. Refer to Section 4.5.5 for details on tumor assessments.

The schedules of activities are provided in Appendix 1 and Appendix 2; the schedule for PK and biosample assessments is presented in Appendix 3.

*The Sponsor may decide to delay, suspend, or terminate enrollment within a given arm. Experimental arms with insufficient clinical activity or unacceptable toxicity will not undergo expansion. New experimental arms may be added during the study by amending the protocol.*

### 3.1.2 Dose-Escalation Phase

The purpose of the dose-escalation phase is to identify the RP2Ds and regimen for idasanutlin and venetoclax when combined with a fixed dose of obinutuzumab in patients with R/R FL and the RP2D for idasanutlin and venetoclax when combined with 375 mg/m$^2$ of rituximab in patients with R/R DLBCL. The RP2Ds will be based on the MTDs of idasanutlin and venetoclax when combined with a fixed dose of obinutuzumab or with 375 mg/m$^2$ of rituximab, but will also take into account all safety data during treatment. There could be two different RP2Ds and/or regimens dependent on the combination of idasanutlin, venetoclax plus obinutuzumab or idasanutlin, and venetoclax plus rituximab.

A minimum of 9 patients and a maximum of 60 patients will be enrolled during the dose-escalation phase. Cohorts of 3–6 patients each will be treated at escalating doses of idasanutlin and venetoclax in accordance with the treatment regimens and dose-escalation rules described in Section 3.1.2.2.

A Bayesian mCRM (see Section 3.1.2.3) is planned to guide the dose-escalation phase to determine the MTD that achieves the efficacious exposure observed. The principle underlying this trial design is the assessment of the dose-toxicity relationship in a safe and efficient manner, allowing for enrollment of patients at subsequent dose levels and/or defining the MTD with robust data, including data for patients from Study BH29812 (obinutuzumab or rituximab in combination with idasanutlin), when available.

Patients will be closely monitored for adverse events during the DLT assessment window, defined as the first two treatment cycles. Adverse events meeting the criteria for

DLT, as defined in Section 3.1.2.1, will be reported to the Sponsor within 24 hours (see Section 5.4.2).

Patients experiencing a DLT during the DLT window (first two cycles of treatment) will permanently discontinue study treatment.

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD assessments and will be replaced by an additional patient at that same dose level. Patients who miss more than one dose of obinutuzumab or rituximab, idasanutlin, or venetoclax during the DLT assessment window for reasons other than a DLT will also be considered non-evaluable and will be replaced.

Additional cohorts may be added following the Sponsor's decision to explore idasanutlin's therapeutic advantage as consolidation or maintenance treatment. The decision for opening such cohorts will be based on long-term safety and tolerability data.

#### 3.1.2.1 Definition of Dose-Limiting Toxicity

In this study, a DLT is defined as at least one of the following events occurring during the first two cycles of treatment and assessed by the investigator as clearly not related to the patient's underlying disease:

- Any Grade 5 adverse event unless unequivocally due to the underlying malignancy or extraneous causes
- Adverse event of any grade that leads to a delay of more than 14 days in the start of the next treatment cycle
- Hematologic adverse events that meet any of the following criteria:
  - Grade 3 or 4 neutropenia in the presence of sustained fever of $>38°C$ (lasting for $>5$ days) or a documented infection
  - Grade 4 neutropenia lasting for $>7$ days *despite adequate supportive care measures. G-CSF may be used to treat Grade ≥3 neutropenia but should not be used as prophylaxis in the DLT period.*
  - Grade 3 or 4 thrombocytopenia if associated with grade ≥ 3 bleeding
  - Grade 4 thrombocytopenia lasting for $>7$ days
- Grade 3 or 4 non-hematologic adverse event, with the following exceptions:
  - Grade 3 or 4 IRRs

    Note that IRRs are not dose-dependent events. They may occur even after a small amount of drug has been administered.
  - Grade 3 laboratory TLS without manifestations of clinical TLS (see Appendix 5 for the Howard-based criteria for clinical and laboratory TLS)
  - Grade 3 AST or ALT increase lasting < 7 days
  - Grade 3 diarrhea that responds to adequate therapy within 48 hours

- Grade 3 nausea or vomiting that occurs in the absence of premedication and responds to adequate therapy within 72 hours
- Grade ≤3 fatigue, asthenia, anorexia, or constipation that resolves to Grade ≤2 in ≤7 days

- Any increase in hepatic transaminase > 3 × baseline AND an increase in direct bilirubin > 2 × ULN, WITHOUT any findings of cholestasis or jaundice or signs of hepatic dysfunction AND in the absence of other contributory factors (e.g., worsening of metastatic disease or concomitant exposure to known hepatotoxic agent or of a documented infectious etiology) is suggestive of potential drug induced liver injury (DILI) (according to Hy's Law) and will be considered a DLT.

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

#### 3.1.2.2 Treatment Regimens and Dose-Escalation Rules Patients with FL and DLBCL until the Bridging cohorts

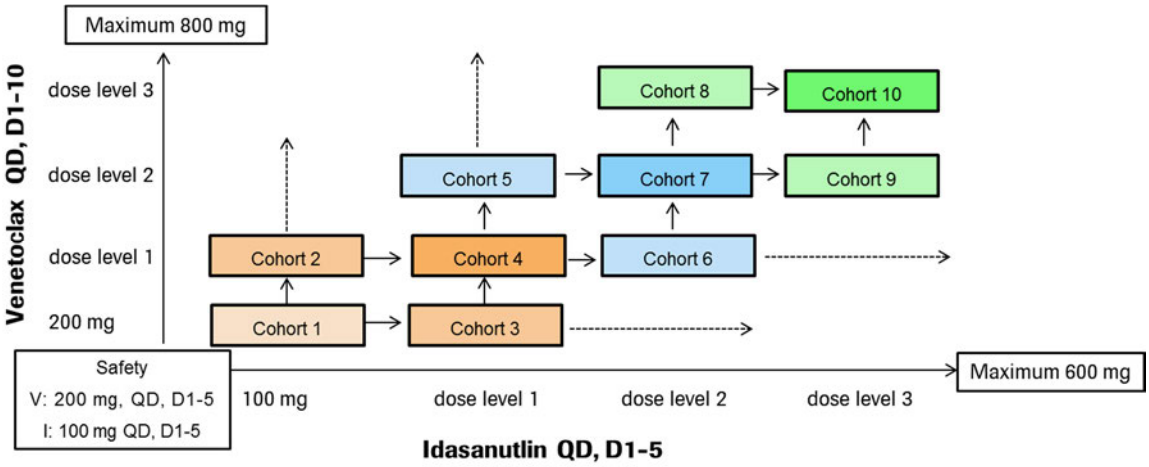
During this first dose-escalation phase, patients will be enrolled according to the schema in Figure 3. Three patients will initially be enrolled in each cohort, and up to 3 additional patients can be enrolled in a cohort at the Sponsor's discretion. The first patient in each cohort will be observed for safety for 1 week after Cycle 1 Day 1 before additional patients are enrolled in the same cohort. A minimum of 3 patients enrolled in a cohort must complete at least the first two cycles (i.e., the DLT assessment window, until Cycle 2, Day 28) before enrollment commences in the next cohort(s). Intra-patient dose escalation is not permitted in this study.

Enrollment will begin in a safety cohort in which patients will be treated at starting doses of 100 mg QD on Days 1–5 of each cycle for idasanutlin and 200 mg QD on Days 1–5 of each cycle for venetoclax, given in combination with obinutuzumab at the standard dose on Days 1, 8, and 15 of Cycle 1 and Day 1 of subsequent cycles (see Figure 3 for details on treatment regimens). If treatment in the safety cohort is well tolerated, treatment will be initiated in Cohort 1 at the same doses as the safety cohort, except that patients will receive venetoclax on Days 1–10 of each cycle (see Figure 3). This regimen is refered to as Regimen A.

If the initial treatment regimen is not tolerated in the safety cohort, any subsequent cohorts will receive venetoclax on Days 1–5 of each cycle.

If safety and tolerability allow, the next two cohorts (Cohorts 2 and 3) will be enrolled concurrently. Patients in Cohort 2 will receive an escalated dose of venetoclax, while patients in Cohort 3 will receive an escalated dose of idasanutlin. Thus, only one drug will be escalated within each of the concurrent cohorts. If safety and tolerability allow, patients in Cohort 4 will receive both venetoclax and idasanutlin at the escalated doses given in the previous two cohorts (see Figure 3).

**Figure 3 Dose-Escalation Schema (Regimen A)**




Obinituzumab or rituximab are given at standard doses.
D1–5 = Days 1–5; D1–10 = Days 1–10; I=idasanutlin; QD = once a day; V = venetoclax.

If TLS is observed in the initial cohorts, venetoclax dosing may be modifed as follows:

- Staggered dosing in which venetoclax may be initiated 2 or 3 days after the first idasanutlin dose during Cycle 1
- Initiation of Cycle 1 treatment below the target dose for venetoclax, followed by incremental dose increases until the target dose is achieved

During this first dose-escalation phase, study treatment will be administered as outlined in Table 1). Patients with FL who achieve a CR or a PR at the EOI will also receive maintenance treatment with obinutuzumab, venetoclax, and idasanutlin. Patients with DLBCL who achieve a CR or a PR at the EOI will also receive consolidation treatment with obinutuzumab, venetoclax, and idasanutlin. Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity for up to 2 years for maintenance treatment and 6 months for consolidation treatment (see Table 2). Patients with DLBCL who achieve a CR based on modified Lugano 2014 criteria at the end of induction (defined as within 6–8 weeks after the start of the last cycle of study treatment) are allowed to proceed to hematopoietic stem cell transplantation if deemed appropriate by the investigator. Such patients will be followed for disease progression and survival. The dose and regimen for venetoclax and idasanutlin will be determined by the Sponsor upon review of all available safety, PK, PD, and efficacy data. The dose for maintenance/consolidation will not exceed the dose the patient received during induction. *The FL and DLBCL bridging cohorts may open at different times, and in this case, the venetoclax dosing regimen (5 vs. 10 days) may be explored independently.*

### Combination of Rituximab, Idasanutlin, and Venetoclax in Patients with DLBCL in the Bridging Cohorts

Following the identification of the MTDs for idasanutlin and venetoclax in combination with obinutuzumab, *or following Sponsor decision based on clinical judgment,* a bridging cohort of patients with DLBCL will be opened to *repeat the last dose tested* in combination with rituximab instead of obinutuzumab (375 mg/m$^2$ on Day 1 of each cycle; see Figure 4 and Table 1).

If safety and tolerability allow, idasanutlin and venetoclax dose escalations may be explored in combination with rituximab in patients with DLBCL until identification of new MTDs (see Figure 4).

### Combination of Obinutuzumab, Idasanutlin, and Venetoclax in Patients with FL in the Bridging Cohorts

Following the identification of the MTDs for idasanutlin and venetoclax in combination with obinutuzumab in Regimen A, *or following Sponsor decision based on clinical judgment,* a bridging cohort of patients with FL will be opened to *repeat the last dose tested* in a different regimen. Obinutuzumab will be given alone in Cycle 1 and in combination with idasanutlin and venetoclax from Cycle 2 to 6 (see Figure 4 and Table 1). This regimen is referred to as Regimen B.

If safety and tolerability allow, idasanutlin and venetoclax dose escalation may be explored with Regimen B in patients with FL until identification of new MTDs (see Figure 4).

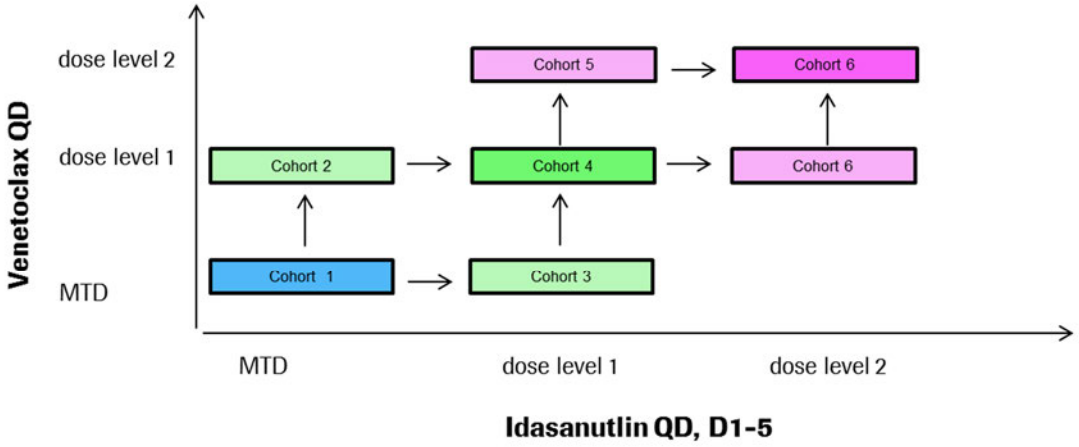
After the last patient in each cohort has completed the two-cycle DLT observation period, the Sponsor, in consultation with the investigators, will evaluate the next dose recommended according to the mCRM (see Section 3.1.2.3) and agree on doses for the subsequent cohort(s), taking into account relevant demographic, adverse event, laboratory, dose administration, and PK (if available) data. At each dose-escalation step, the dose may be escalated or de-escalated, or an additional cohort at the same dose level may be enrolled.

On the basis of review of real-time safety data from this study and all available data from Study BH29812, dose escalation may be halted or modified by the Sponsor as deemed appropriate.

Although the DLT assessment window is defined as the first two treatment cycles, cumulative toxicities occurring beyond the first two cycles may be considered when determining the MTDs for idasanutlin or venetoclax.

Multiple MTDs may be identified, and the most appropriate RP2Ds will be chosen on the basis of safety, PK, and PD data. At the end of dose–escalation phase, RP2Ds (one for idasanutlin and one for venetoclax) in combination with obinutuzumab and one regimen will be decided for patients with FL. RP2Ds (one for idasanutlin and one for venetoclax) in combination with rituximab will be decided for patients with DLBCL. The RP2Ds of idasanutlin and venetoclax, as well as the treatment regimens for patients with FL and DLBCL, may be different.

**Figure 4 Dose-Escalation Schema in Bridging Cohorts**




**Rituximab is given at standard dose in DLBCL cohorts**
**Obinutuzumab is given at standard dose in FL cohorts and follows Regimen B schedule**

D1–5 = Days 1–5; I=idasanutlin; QD = once a day; MTD = maximum tolerated dose; V = venetoclax.

## Table 1 Induction Treatment during the Dose-Escalation Phase for Patients with Follicular Lymphoma and DLBCL

| Cycle(s) | **Safety Cohort (28-Day Cycles):** Regimen A | **Cohort 1 (28-Day Cycles):** Regimen A |
|---|---|---|
| Cycle 1 | • Obinutuzumab 1000 mg IV on Days 1, 8, and 15<br>• Idasanutlin 100 mg QD orally on Days 1–5<br>• Venetoclax 200 mg QD orally on Days 1–5 | • Obinutuzumab 1000 mg IV on Days 1, 8, and 15<br>• Idasanutlin 100 mg QD orally on Days 1–5<br>• Venetoclax 200 mg QD orally on Days 1–10 |
| Cycles 2–6 | • Obinutuzumab 1000 mg IV on Day 1<br>• Idasanutlin 100 mg QD orally on Days 1–5<br>• Venetoclax 200 mg QD orally on Days 1–5 | • Obinutuzumab 1000 mg IV on Day 1<br>• Idasanutlin 100 mg QD orally on Days 1–5<br>• Venetoclax 200 mg QD orally on Days 1–10 |
| | **Cohort 2 (28-Day Cycles):** Regimen A | **Cohort 3 (28-Day Cycles):** Regimen A |
| Cycle 1 | • Obinutuzumab 1000 mg IV on Days 1, 8, and 15<br>• Idasanutlin 100 mg QD orally on Days 1–5<br>• Venetoclax TBD QD orally on Days 1–10 | • Obinutuzumab 1000 mg IV on Days 1, 8, and 15<br>• Idasanutlin TBD QD orally on Days 1–5<br>• Venetoclax 200 mg QD orally on Days 1–10 |
| Cycles 2–6 | • Obinutuzumab 1000 mg IV on Day 1<br>• Idasanutlin 100 mg QD orally on Days 1–5<br>• Venetoclax TBD QD orally on Days 1–10 | • Obinutuzumab 1000 mg IV on Day 1<br>• Idasanutlin TBD QD orally on Days 1–5<br>• Venetoclax 200 mg QD orally on Days 1–10 |
| | **Cohort 4 and Subsequent Cohorts (28-Day Cycles):** Regimen A | |
| Cycle 1 | • Obinutuzumab 1000 mg IV on Days 1, 8, and 15<br>• Idasanutlin TBD QD orally on Days 1–5<br>• Venetoclax TBD QD orally on Days 1–10 | |
| Cycles 2–6 | • Obinutuzumab 1000 mg IV on Day 1<br>• Idasanutlin TBD QD orally on Days 1–5<br>• Venetoclax TBD QD orally on Days 1–10 | |
| | **Bridging Cohorts, Patients with DLBCL Only** (28-Day Cycles) | |
| Cycles 1–6 | • Rituximab 375 mg/m$^2$ IV on Day 1<br>• Idasanutlin, oral Days 1–5, starting dose MTD identified in combination with obinutuzumab and venetoclax, minimal clinically and pharmacologically feasible dose-escalation steps 50 mg<br>• Venetoclax, oral, starting dose and regimen MTD identified in combination with obinutuzumab and idasanutlin, minimal clinically and pharmacologically feasible dose-escalation steps 100 mg | |

**Table 1 Induction Treatment during the Dose-Escalation Phase for Patients with Follicular Lymphoma and DLBCL (cont.)**

| | **Bridging Cohorts, Patients with Follicular Lymphoma Only (28-Day Cycles):** Regimen B |
|---|---|
| Cycle 1 | • Obinutuzumab 1000 mg IV on Days 1, 8, and 15 |
| Cycle 2–6 | • Obinutuzumab 1000 mg IV on Day 1<br>• Idasanutlin, oral Days 1–5, starting dose MTD identified in combination with obinutuzumab and venetoclax, minimal clinically and pharmacologically feasible dose-escalation steps 50 mg<br>• Venetoclax, oral, starting dose and regimen MTD identified in combination with obinutuzumab and idasanutlin, minimal clinically and pharmacologically feasible dose-escalation steps 100 mg |

DLBCL = diffuse large B-cell lymphoma; IV = intravenous; MTD = maximum tolerated dose; QD = once a day; TBD = to be determined.

**Table 2 Post-Induction Treatment during the Dose-Escalation Phase**

| | Post-Induction Treatment |
|---|---|
| Patients with FL | Maintenance treatment consisting of the following:<br>• Obinutuzumab 1000 mg IV every 2 months for 24 months<br>• Venetoclax for 6 months [a]<br>• Idasanutlin for 6 months [a] |
| Patients with DLBCL | Consolidation treatment consisting of the following, administered for 6 months [b]:<br>• Obinutuzumab 1000 mg IV every 2 months for 6 months<br>• Or Rituximab 375 mg/m$^2$ IV on Day 1 every 2 months for 6 months<br>• Venetoclax for 6 months [a]<br>• Idasanutlin for 6 months [a] |

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

[a] Dose and regimen to be determined by the Sponsor after review of all relevant data. The dose for maintenance/consolidation will not exceed the dose the patient received during induction.

[b] Patients will receive obinutuzumab or rituximab according to study treatment received in the induction.

### 3.1.2.3 Use of Modified Continual Reassessment Model for Dose and MTD Determination

The dose escalation will employ a mCRM with overdose control design in order to define the MTD and/or the recommended dose for subsequent cohorts.

The design is based on the primary safety variable, that is, the occurrence of a DLT. The MTD is defined as the dose that maximizes the probability of achieving a DLT rate of 16%–33% (target toxicity interval) and results in a $<35\%$ probability of having a DLT rate of $>33\%$ (overdose control).

The maximum allowable increments for idasanutlin from the highest dose already tested will not exceed 100 mg, with a minimum increase of 50 mg. The maximum allowable increments for venetoclax from the highest dose already tested will not exceed 200 mg, with a minimum increase of 100 mg.

In addition, the dose of idasanutlin will not be escalated above 600 mg and the dose of venetoclax will not be escalated above 800 mg. The selection of the next dose will be subject to clinical judgment and mandated safety constraints that limit the size of the dose increments. Clinical judgment will always override mCRM recommendations in the dose-selection process.

A detailed algorithm for the selection of the next recommended combination of doses in the dose-escalation procedure is described in Appendix 6. As stated above, only combinations of doses with a $<35\%$ probability of having a DLT rate of $>33\%$ will be allowed.

Dose escalation will stop when the maximum allowed sample size, 60 patients, has been reached or there is enough confidence in the prediction of the MTD (e.g., at least 6 patients have been recruited at the MTD doses and there is a $>40\%$ probability of having a DLT rate of 16%–33%).

The following two marginal models (two-parameter logistic regression), which describe the relationship between DLT and idasanutlin dose in the absence of venetoclax, and conversely, the relationship between DLT and venetoclax dose in the absence of idasanutlin, were considered:

$$logit\left(p\left(d^*_{IDA,i}\right)\right) = \alpha_1 + \beta_1 log\left(d^*_{IDA,i}\right) \quad (1)$$

$$logit\left(q\left(d^*_{VEN,i}\right)\right) = \alpha_2 + \beta_2 log\left(d^*_{VEN,i}\right) \quad (2)$$

In the first model, $\alpha_1$ and $\beta_1$ are model parameters and $p(d^*_{IDA,i})$ is the probability of experiencing a DLT at a dose $d^*_{IDA,i}$ of idasanutlin, in the absence of venetoclax, with $d^*_{IDA,i} = \frac{d_{IDA,i}}{d^{REF}_{IDA}}$ being the normalized idasanutlin dose using the reference dose $d^{REF}_{IDA} = 200$ mg. Similarly, in the second model, $\boldsymbol{\alpha_2}$ and $\boldsymbol{\beta_2}$ are model parameters and $q(d^*_{VEN,i})$ is the probability of experiencing a DLT at a dose $d^*_{VEN,i}$ of venetoclax, in the absence of idasanutlin, with $d^*_{VEN,i} = \frac{d_{VEN,i}}{d^{REF}_{VEN}}$ being the normalized venetoclax dose using the reference dose $d^{REF}_{VEN} = 400$ mg.

In order to define the prior distributions (priors) for the parameters of the two marginal models, the Sponsor's clinical team went through a process of prior elicitation, based on expert knowledge and previous data (i.e., Study GO27878 for venetoclax and Study NP27872 for idasanutlin), to reach a consensus on the questions listed in Table 3.

**Table 3 Prior Elicitation**

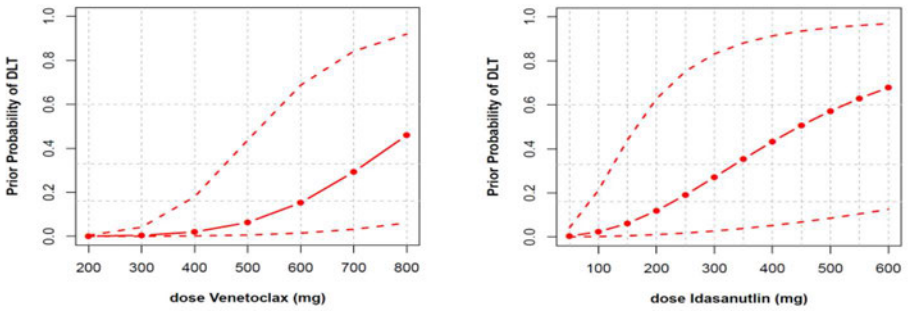
| | Question | Idasanutlin with Obinutuzumab | Venetoclax with Obinutuzumab |
|---|---|---|---|
| 1 | What would be considered a negligible DLT rate? | 16% | |
| 2 | What would be considered a target DLT rate? | 33% | |
| 3 | What would be considered an unacceptable DLT rate? | 60% | |
| 4 | What is the highest dose known (i.e., almost certain) to have a negligible DLT rate (as per Question 1 above)? | 100 mg | 400 mg |
| 5 | What dose is thought to have an unacceptable DLT rate (as per Question 3 above)? | 550 mg | 900 mg |
| 6 | What is the smallest dose known (i.e., almost certain) to have a DLT rate above the target rate (as per Question 2 above)? | 800 mg | 1000 mg |
| 7 | What dose is thought to have a target DLT rate (as per Question 2 above)? | 300 mg | 700 mg |

Based on the answers from Table 3, the following priors were defined:

$$\begin{bmatrix} \alpha_1 \\ log(\beta_1) \end{bmatrix} \sim N\left[\begin{pmatrix} -2.0 \\ 0.916 \end{pmatrix}, \begin{pmatrix} 1.665 & 0.037 \\ 0.037 & 0.002 \end{pmatrix}\right]$$
$$\begin{bmatrix} \alpha_2 \\ log(\beta_2) \end{bmatrix} \sim N\left[\begin{pmatrix} -3.905 \\ 1.685 \end{pmatrix}, \begin{pmatrix} 1.47 & 0.0299 \\ 0.0299 & 0.003 \end{pmatrix}\right]$$

A visual representation of the priors for the two marginal models is provided in Figure 5.

## Figure 5 Margins for Venetoclax and Idasanutlin




DLT = dose-limiting toxicity.

Given the marginal models introduced in (1) and (2), the probability of DLT for a dose combination of idasanutlin and venetoclax in case of "no interaction" would be as follows:

$$p^0(p,q) = p + q - pq$$

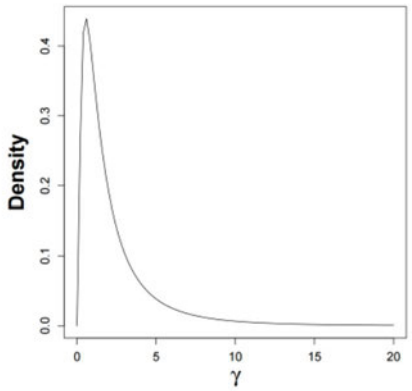
The probability of DLT $p(p,q,\gamma)$ for a dose combination of idasanutlin and venetoclax is parameterized as follows:

$$\frac{\pi}{1-\pi} = \frac{\pi^0}{1-\pi^0} \cdot exp(\gamma \cdot d^*_{IDA} \cdot d^*_{VEN})$$

with the interaction between idasanutlin and venetoclax modeled through the interaction parameter $\gamma$.

The interpretation of the interaction parameter $\gamma$ is the log of the ratio of the odds under interaction and no interaction, at the line where $d^*_{IDA} \cdot d^*_{VEN} = 1$. Hence, no interaction is attained with $\gamma = 0$, synergy is attained with $\gamma > 0$, and antagonism is attained with $\gamma < 0$. A log-normal prior for $\gamma$ ( $log(\gamma) \sim N(\mu = 0.4, \sigma = 1.0)$) was used to allow only for synergistic effect between the two drugs (see Figure 6).

**Figure 6 Marginal Priors for Venetoclax and Idasanutlin**




The operating characteristics of the proposed mCRM were carefully evaluated through the use of simulations across different scenarios, and the results are reported in Appendix 6. The general conclusion is that the current design provides, with an assumed sample size of 42 patients, overall good performances in selecting the correct MTD, while at the same time limiting the amount of overdosing across all scenarios.

During the study, DLT data will become available from the ongoing Phase Ib/II study BH29812, which is currently evaluating the safety and efficacy of obinutuzumab in combination with idasanutlin, and these data may be added to the BH39147 DLT data.

The above described mCRM algorithm will be first used for predicting the MTD in the combined FL/DLBCL dose-escalation cohorts where idasanutlin and venetoclax are given in combination with obinutuzumab. A similar mCRM will be then employed to support dose escalation in the DLBCL bridging cohorts where idasanutlin and venetoclax are given in combination with rituximab, if applicable, and in the FL bridging cohorts where idasanutlin and venetoclax are given in combination with obinutuzumab using a different regimen (Regimen B), if applicable.

In the event that more than one dose schedule for venetoclax will be explored during dose escalation (e.g., Days 1–5 and Days 1–10), independent mCRM models (with the same priors as described above) will be used for the different dose schedules. However a more complex mCRM, making use of all data (jointly modeling the different dose schedules) may be considered as well.

### 3.1.3 Expansion Phase

The expansion phase is designed to further assess the safety and efficacy of idasanutlin and venetoclax given in combination with obinutuzumab at their respective RP2Ds in patients with R/R FL and of rituximab in combination with idasanutlin and venetoclax at their respective RP2Ds in patients with R/R DLBCL. Approximately 80 patients (40 patients with FL and 40 patients with DLBCL) will be enrolled during the expansion

phase and treated as described below.  An interim futility analysis using a predictive probability design may be performed during the expansion phase. The start of the expansion phase may not happen simultaneously for the two indications.

All patients will receive induction treatment as outlined in Table 4.

## Table 4 Induction Treatment for the Expansion Phase

| Triplet Dose: FL Cohort (28-Day Cycles) | | | |
|---|---|---|---|
| | Regimen A [a] | | Regimen B [a] |
| Cycle 1 | • Obinutuzumab 1000 mg IV on Days 1, 8, and 15<br>• Idasanutlin QD orally at the RP2D in combination with obinutuzumab on Days 1–5 [a]<br>• Venetoclax QD orally at the RP2D in combination with obinutuzumab, with regimen determined in the dose-escalation phase (on Days 1–5 or Days 1–10) [a] | Cycle 1 | • Obinutuzumab 1000 mg IV on Days 1, 8, and 15 |
| Cycles 2–6 | • Obinutuzumab 1000 mg IV on Day 1<br>• Idasanutlin QD orally at the RP2D in combination with obinutuzumab on Days 1–5<br>• Venetoclax QD orally at the RP2D in combination with obinutuzumab, with regimen determined in the dose-escalation phase (Days 1–5 or Days 1–10) | Cycles 2–6 | • Obinutuzumab 1000 mg IV on Day 1<br>• Idasanutlin QD orally at the RP2D in combination with obinutuzumab on Days 1–5<br>• Venetoclax QD orally at the RP2D in combination with obinutuzumab, with regimen determined in the dose-escalation phase (Days 1–5 or Days 1–10) |
| **Triplet Dose: DLBCL Cohort (28-Day Cycles)** | | | |
| Cycles 1–6 | • Rituximab 375 mg/m$^2$ IV on Day 1<br>• Idasanutlin QD orally at the RP2D in combination with rituximab on Days 1–5<br>• Venetoclax QD orally at the RP2D in combination with rituximab, with regimen determined in the dose-escalation phase (on Days 1–5 or Days 1–10) | | |

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; IV = intravenous; QD = once a day; RP2D = recommended Phase II dose.

[a] The treatment regimen will be determined at the end of dose-escalation phase.

Patients with FL who achieve a CR or a PR at the EOI will receive maintenance treatment with obinutuzumab, venetoclax, and idasanutlin. Patients with DLBCL who achieve a CR or PR at the EOI will receive consolidation treatment with rituximab, venetoclax, and idasanutlin. Post-induction treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity for up to 2 years for maintenance treatment and 6 months for consolidation treatment (see Table 5). Patients with DLBCL who achieve a CR based on modified Lugano 2014 criteria at the end of induction (defined as within 6–8 weeks after the start of the last cycle of study treatment) are allowed to proceed to hematopoietic stem cell transplantation if deemed appropriate by the investigator.

**Table 5 Post-Induction Treatment for the Expansion Phase**

| | Post-Induction Treatment |
|---|---|
| Patients with FL | Maintenance treatment consisting of the following:<br>• Obinutuzumab 1000 mg IV every 2 months for 24 months<br>• Venetoclax for 6 months [a]<br>• Idasanutlin for 6 months [a] |
| Patients with DLBCL | Consolidation treatment consisting of the following, administered for 6 months:<br>• Rituximab 375 mg/m$^2$ IV every 2 months for 6 months<br>• Venetoclax for 6 months [a]<br>• Idasanutlin for 6 months [a] |

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

[a] Dose and regimen to be determined by the Sponsor after review of all relevant data. The dose for maintenance/consolidation will not exceed the dose the patient received during induction.

### 3.1.4 Internal Monitoring Committee

An IMC will monitor patient safety throughout the study. The IMC will include Sponsor representatives from Clinical Science, Drug Safety, Biostatistics, and Statistical Programming and Analysis. In addition to the ongoing assessment of the incidence and nature of adverse events (particularly, Grade ≥3 events), serious adverse events, deaths, and laboratory abnormalities performed by the investigator and the Medical Monitor, the IMC will review all necessary cumulative data, including data required for determination of the RP2Ds, at regular intervals during the study and will also review results from the interim analysis of efficacy data. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, additional analyses should be performed, enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any potential new safety signals. Specific operational details such as the committee's composition, frequency and timing of

meetings, members' roles and responsibilities, and data to be reviewed will be detailed in an IMC charter.

### 3.1.5 Independent Review Committee

An IRC will assess all patients for response on the basis of imaging results, bone marrow biopsy results, and relevant clinical data. The review will consist of two parts: a radiology review and an oncology review. The IRC will consist of radiologists, nuclear medicine experts, and a board-certified oncologist with experience in malignant lymphoma. Specific methodological and operational details will be specified in the IRC charter.

### 3.1.6 Post-Treatment Follow-Up and Survival Follow-Up

Patients who complete treatment or discontinue treatment for reasons other than disease progression will undergo assessments every 3 months during the post-treatment follow-up period, which will continue until disease progression, the start of new anti-lymphoma treatment, or the end of the study (as defined below), whichever occurs first. Patients who experience disease progression will be evaluated for survival status and initiation of new anti-lymphoma treatment every 3 months until the end of the study. Details are provided in the schedules of activities (see Appendix 1 and Appendix 2).

## 3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the time when both of the following conditions are met:

- All enrolled patients with FL have completed or discontinued study treatment (including induction and maintenance, as applicable)
- All enrolled patients with DLBCL have been followed for at least 1 year after they have completed or discontinued study treatment (including induction and consolidation, as applicable).

The total length of the study is expected to be approximately 48 months.

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Treatment Combination

As discussed in Section 1.1.1, despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, FL remains essentially an incurable disease. Patients invariably relapse, and active and well-tolerated agents are needed following relapse. DLBCL can be cured in $>$50% of cases; however, up to one-third of patients have refractory disease or relapse after treatment. Success rates with salvage therapy and autologous transplantation are poor, which highlights the urgent need for novel therapeutic approaches for these patients.

On the basis of a compelling biologic and clinical rationale, as presented in Section 1.5, the addition of venetoclax and idasanutlin to obinutuzumab or rituximab is a promising

approach to increase the number of patients with R/R FL and DLBCL who achieve remission and to prolong the duration of response in these patients.

Obinutuzumab and rituximab are effective in the treatment of B-cell malignancies on the basis of their anti-CD20 mechanisms of action leading to direct cell death. The majority of B-lymphoid malignancies, including NHL and CLL, also express wild-type p53 (Imamura et al. 1994).

MDM2 regulates p53 through a negative feedback loop. However, in cancer cells overexpressing MDM2, this feedback loop is deregulated. Therefore, blocking the p53–MDM2 interaction is expected to overcome the oncogenic consequences of MDM2 overproduction and to restore p53 function (Ray-Coquard et al. 2012).

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in FL, where the t(14;18) chromosomal translocation results in significant overexpression of the protein in B cells. Bcl-2 overexpression is a major contributor to the pathogenesis of many types of lymphoid malignancies and has been implicated as a cause of chemotherapy resistance.

The non-overlapping and complementary mechanisms of action of obinutuzumab or rituximab (direct tumor cell death) on one hand and idasanutlin and venetoclax (increased apoptosis) on the other may provide superior efficacy in treating B-lymphoid malignancies. In addition, complementary mechanisms of action of venetoclax and idasanutlin may allow overcoming resistances that may develop during treatments with monotherapies.

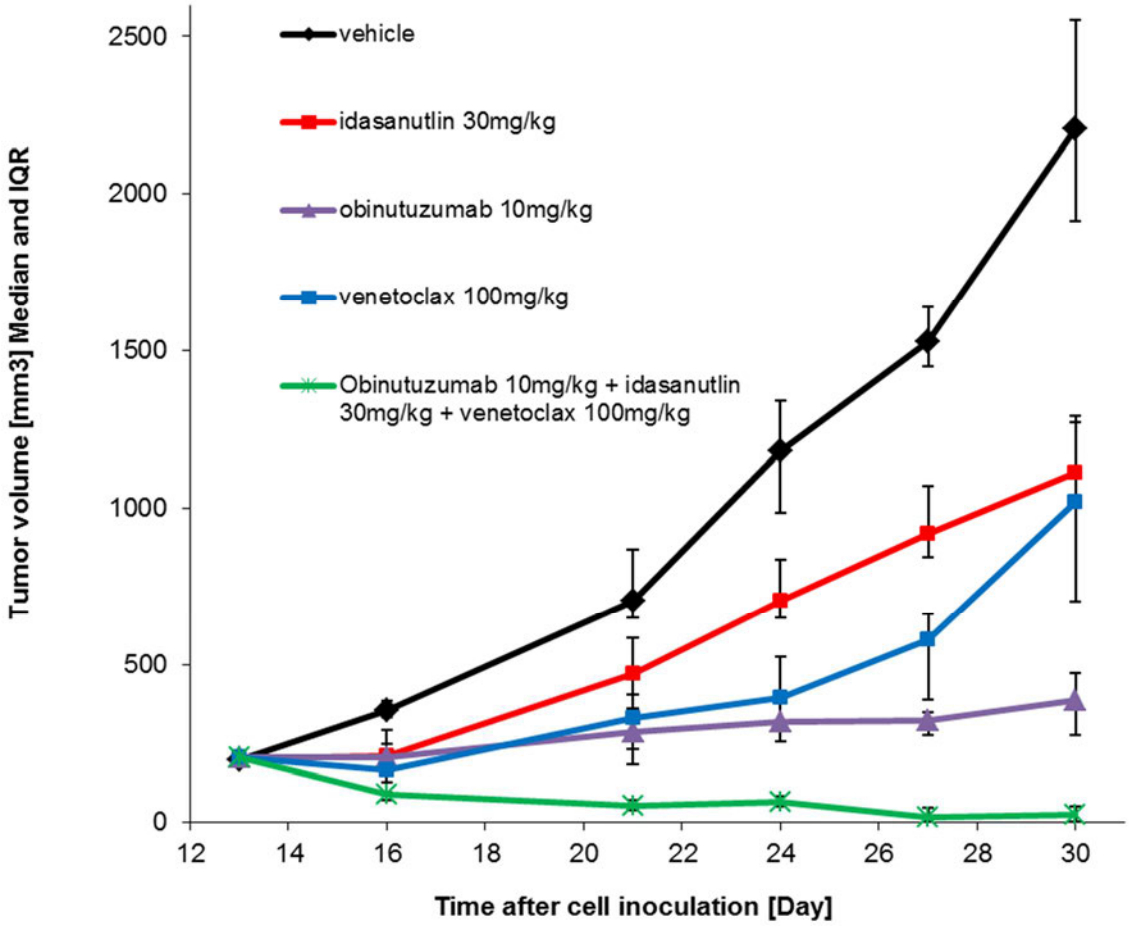
In in vitro assays, both idasanutlin and venetoclax induced concentration-dependent apoptosis in a DLBCL cell line (DOHH-2) and in an MCL cell line (Z-138), and the combination with obinutuzumab or rituximab further enhanced cell-death induction.

Importantly, idasanutlin neither influenced obinutuzumab/rituximab–mediated ADCC activity nor B-cell depletion in healthy human whole blood at concentrations of up to 1000 nM and did not affect obinutuzumab/rituximab–mediated NK cell activation (Herting et al. 2014; Herting et al.2016). Similar experiments have been conducted with venetoclax with the same conclusions (Sampath et al. 2013).

In vivo single-agent and combination therapy, the efficacy (inhibition of tumor growth) of obinutuzumab, venetoclax, and idasanutlin was assessed in three NHL xenograft models.

In the in vivo study using the DOHH-2 DLBCL xenograft model, evaluating the triple combination versus respective monotherapies, the combination of obinutuzumab, venetoclax, and idasanutlin resulted in superior efficacy (115% TGI) and tumor regression (TGI $>$ 100%) (see Figure 7).

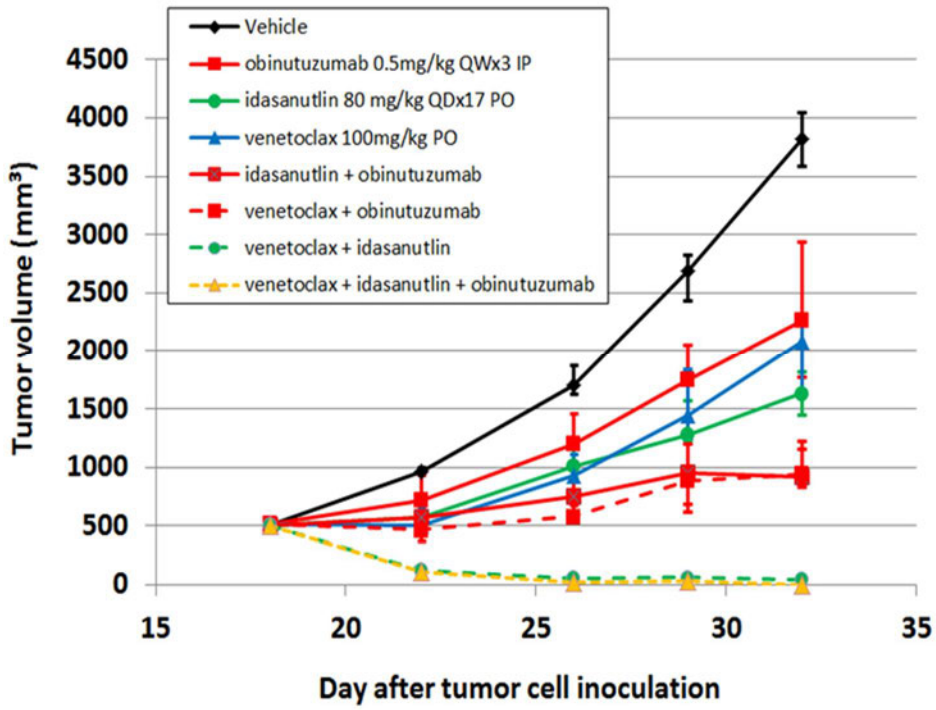
**Figure 7 DOHH-2 DLBCL Xenograft Model: Tumor Volume Analysis**




DLBCL = diffuse large B-cell lymphoma; IQR = interquartile range.

In a Z-138 MCL xenograft study, tumor-bearing SCID beige mice received a suboptimal dose of 0.5 mg/kg obinutuzumab administered intraperitoneally QD with the idasanutlin MBP formulation given orally QD at 80 mg/kg dose (initially, 100 mg/kg for 3 days). Mice were dosed with 100 mg/kg of venetoclax orally QD. Treatment with obinutuzumab, idasanutlin, and venetoclax monotherapy was significantly active resulting in TGI of 47 %, 67%, and 53%, respectively. The combination of obinutuzumab with idasanutlin or venetoclax resulted in 86% and 85% TGI, respectively. The combination groups of idasanutlin and venetoclax and also the triple combination with obinutuzumab showed superiority compared with monotherapy treatment, resulting in tumor regression of Z-138 xenograft tumors (see Figure 8).

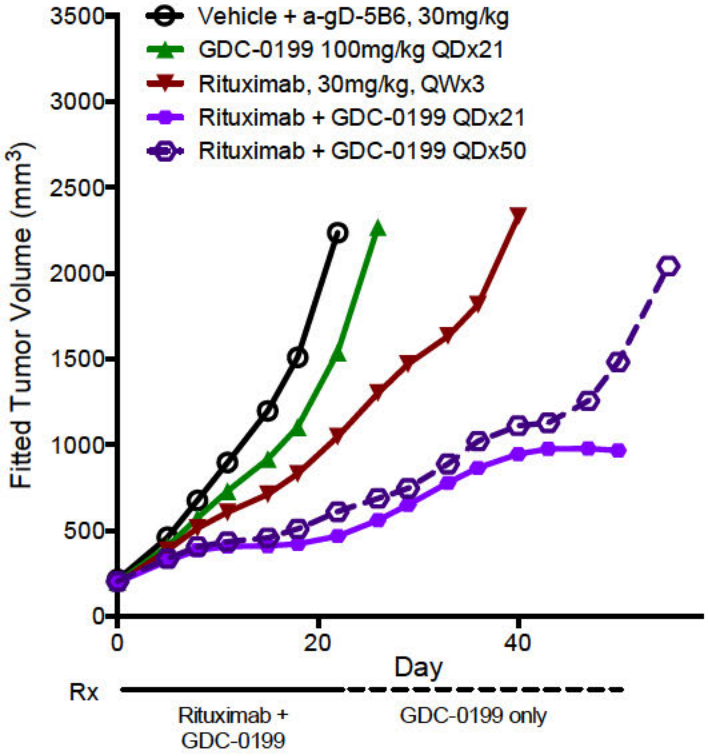
**Figure 8 Z-138 MCL Xenograft Model: Tumor Growth Inhibition Analysis**




MCL = mantle-cell lymphoma; PO = by mouth; QD = once a day; QW = once a week.

The efficacy of venetoclax (GDC-0199) in combination with rituximab was also evaluated in vivo in a WSU-DLCL2 xenograft model (DLBCL). When compared to treatment with rituximab, venetoclax as a single agent dosed orally and daily was less efficacious in the WSU-DLCL2 xenograft model (see Figure 9). However, the combination of venetoclax with rituximab resulted in sustained in vivo efficacy and increased duration of response (see Figure 9).

**Figure 9 WSU-DLCL2 Xenograft Model: Tumor Volume Analysis**

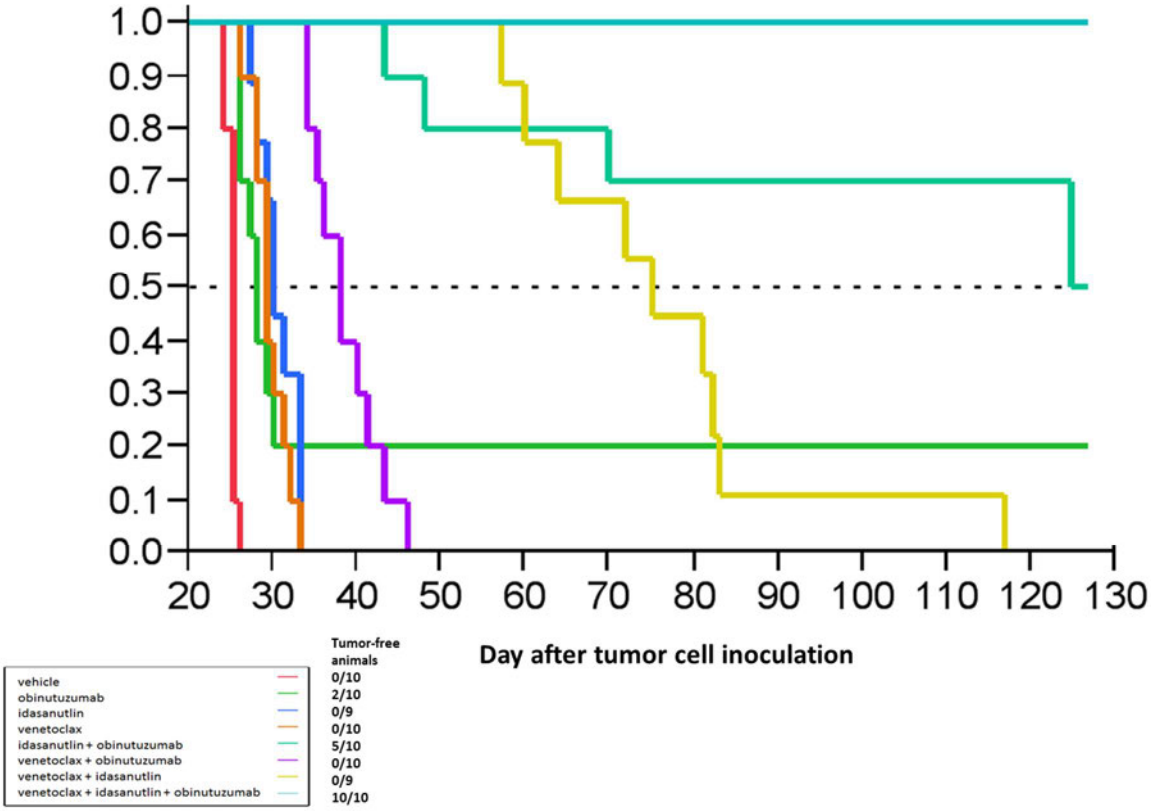



IV = intravenous; QD = once a day; QW = once a week; Rx = treatment.

Notes: Venetoclax (GDC-0199) dosed orally and rituximab dosed IV at the doses indicated. Vehicles (60% phosal) + 30 mg/kg anti-IgD. All doses of drugs were well tolerated based on minimal changes in animal body weights. Rx: Solid line indicates treatment period for drug combinations and dashed lines indicates treatment with venetoclax (GDC-0199) only following combination therapies.

The superiority of the combination treatment was also shown in a time-to-event analysis. The triple combination treatment showed the best response, with a median time-to-event of approximately > 125 days. In all animals in this group, the tumor disappeared and did not return during the observation time (125 days) (see Figure 10).

**Figure 10 Z-138 Xenograft Model: Time-to-Event Analysis**




Caution should be used when interpreting any mouse toxicology data. It is important to note that none of the mice experienced more than a 20% change in body weight, weight being the only useful toxicology parameter in a xenograft model, and no obvious potential drug-related adverse events were observed.

In summary, nonclinical in vitro and in vivo data strongly support the investigation of obinutuzumab or rituximab, venetoclax, and idasanutlin combination therapy in clinical studies.

Owing to the varying sensitivity of the respective cell lines in vivo (e.g., strong single-agent activity of obinutuzumab in the Z-138 model) and the need to still be able to show a combination effect, tumor-bearing SCID beige mice received a suboptimal dose of 0.5 mg/kg for obinutuzumab administered intraperitoneally QD with idasanutlin MBP formulation given orally (PO) QD at 80 mg/kg (initially, 100 mg/kg for 3 days) dose for the Z-138 model, whereas doses of 10 mg/kg obinutuzumab with idasanutlin at 30 mg/kg were chosen for the DOHH-2 model. Doses of 100 mg/kg of venetoclax PO QD were used for both models.

All compounds, given as a single agent, demonstrated significant anti-tumor efficacy. The triple combination showed superiority over monotherapy treatment, resulting in tumor regression of both xenograft tumors in a time-to-event analysis. To minimize the animal handling for multiple blood sampling, no direct pharmacokinetics for any of the three compounds were measured in the two NHL xenograft models studied.

Serum trough levels of obinutuzumab are projected to be approximately 5 and 60 μg/mL, respectively, corresponding to weekly doses of 0.5 and 10 mg/kg (Obinutuzumab Investigator's Brochure). The obinutuzumab dose in the present clinical study is 1000 mg, yielding mean serum trough concentration levels of obinutuzumab, ranging from 180 to 201 μg/mL at steady state (Obinutuzumab Investigator's Brochure), which can easily surpass the exposure in animal models.

The venetoclax exposure corresponded to an AUC $\geq$ 28.8 μg • hr/mL, and $C_{max}$ $>$ 2.74 μg/mL was reached following a single dose of 25 mg/kg of venetoclax and to an AUC of 31.2 μg • hr/mL and a $C_{max}$ of 3.83 μg/mL after 100 mg/kg of venetoclax, respectively (Venetoclax Investigator's Brochure); no accumulation was observed in mice following repeated doses. In patients, following multiple oral administrations under fed conditions, venetoclax steady-state AUC increased proportionally over the dose range of 150–800 mg. Under low-fat meal conditions, venetoclax mean steady-state $C_{max}$ was 2.1 μg/mL and $AUC_{0\text{-}24hr}$ was 32.8 μg • hr/mL at the 400 mg QD dose. A significantly higher dose might be required to achieve the intended efficacy for venetoclax in the current clinical study.

Daily oral administration of idasanutlin at 30 mg/kg for 13 days in the DOHH-2 B-cell NHL mouse xenograft model corresponded to a cycle AUC of about 520 μg • hr/mL in combination with 100 mg/kg of venetoclax and obinutuzumab or 450 μg • hr/mL if given alone (SDP formulation).

Daily oral administration of idasanutlin 30 mg/kg and 80 mg/kg in the Z-138 MCL xenograft model corresponded to a cycle AUC of approximately 400 and 1200 μg • hr/mL (MBP formulation), respectively, for a QD $\times$ 5-day dosing schedule. With the SDP formulation to be used in patients, these exposures can be achieved with 300 mg/day and 900 mg/day, respectively.

### 3.3.2 Rationale for Dosing Regimen

#### 3.3.2.1 Rationale for Obinutuzumab and Rituximab Dosing Regimen

The dose and schedule of obinutuzumab in the induction regimen will be 1000 mg administered to patients intravenously on Days 1, 8, and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle (Cycles 2–6). This is based on the recommended dose and schedule (six to eight cycles, depending on the trial) of obinutuzumab in the ongoing Phase III program in patients with NHL (Obinutuzumab Investigator's Brochure). In this study, patients will be treated for six cycles during the induction phase.

The dose and schedule of obinutuzumab in the maintenance regimen (FL) will be 1000 mg administered intravenously to patients every 2 months for up to 2 years. This dosing regimen is based on the obinutuzumab maintenance regimen that was administered in the Phase III study GAO4753g (Trněný et al. 2016). The dose and schedule of obinutuzumab in the consolidation regimen (DLBCL) will be 1000 mg administered intravenously to patients every 2 months for up to 6 months. The consolidation regimen is modeled after the FL maintenance regimen. The rationale for treatment duration is provided in Section 3.3.2.4.

The study will start with obinutuzumab standard dosing in combination with idasanutlin and venetoclax in Cycles 1–6 (Regimen A). For patients with FL, an alternative dosing regimen (Regimen B) with obinutuzumab given at Cycle 1 followed by obinutuzumab in combination with idasanutlin and venetoclax in Cycles 2–6 will be explored to investigate the possibility of alleviating hematological toxicities at Cycle 1. The rationale for exploring Regimen B in patients with FL is that obinutuzumab is given 3 times during Cycle 1 (Days 1, 8, and 15) compared to only at Day 1 in subsequent cycles. Those 3 doses of obinutuzumab, when combined with idasanutlin and venetoclax at higher doses in the same treatment cycle, may induce more profound hematologic toxicities. Staggered idasanutlin and venetoclax dosing to start at Cycle 2 may mitigate toxicities and allow recovery before dosing with the combination. Only one regimen will be chosen for the expansion phase.

For patients with DLBCL in the bridging cohort(s) and the expansion phase, the dose and schedule of rituximab in the induction regimen will be 375 mg/m$^2$ on Day 1 of each 28-day cycle (Cycles 1–6); and the dose and schedule in the maintenance or consolidation phase will be 375 mg/m$^2$ every 2 months. This dose is the recommended dose in NHL population and is the standard of care. For patients receiving rituximab, no alternative regimen will be explored as rituximab is only given at Day 1 in each treatment cycle and the overlapping toxicities with idasanutlin are expected to be less pronounced.

#### 3.3.2.2 Rationale for Idasanutlin Dosing Regimen

Based on data from Studies NP27872 and NP28679 in solid tumors and AML, the first PD signal was detected at an $AUC_{24hr}$ between 50 and 60 μg • hr/mL. For the QD × 5-day regimen, 55 μg • hr/mL (55000 ng • hr/mL) corresponds to a daily dose of approximately 100 mg of idasanutlin.

In addition, safety data are available for patients with solid tumors and NHL who received idasanutlin. For the 100-mg QD × 5-day schedule, no Grade 3 or 4 hematologic or related GI toxicities were observed.

Therefore, a daily dose of 100 mg of the idasanutlin SDP has been chosen as a safe starting dose with potential to activate p53 as determined by the MIC-1 PD marker in combination with obinutuzumab and venetoclax.

Idasanutlin PK exposure, PD effects (e.g., MIC-1, a p53 activation marker), and target-mediated hematologic changes (platelet reduction, in particular) were evaluated to support the optimal dosing schedule. Weekly, 3-day, and 5-day schedules were tested, with weekly higher doses not activating the PD marker MIC-1. The 3-day dosing did not achieve steady state and did not alleviate thrombocytopenia; therefore, a 5-day schedule was chosen.

Extended dosing of idasanutlin for up to 1 year in total with obinutuzumab or rituximab and venetoclax will allow exploration of whether additional activity is observed during the extended (post-induction) dosing period.

#### 3.3.2.3 Rationale for Venetoclax Dosing Regimen

Venetoclax dosing for this study is based on experience from the Phase I study (M12-175) with single-agent venetoclax in patients with R/R NHL and from the Phase Ib study (M12-630) of venetoclax in combination with BR in patients with R/R NHL. In NHL, all responses in patients with FL have occurred at doses $\geq$600 mg QD. Although nonclinical data exist for synergistic activity at a dose equivalent to 400 mg QD (Souers et al. 2013), it is desirable to give venetoclax at the higher doses at which single-agent activity has been observed.

The M12-175 study explored a step-up dosing schedule in order to safely administer venetoclax by reducing the risk of TLS. The study showed safety of initial doses of up to 400 mg without clinically significant TLS in patients with NHL. Patients with NHL have received single-agent target doses of 1200 mg without DLTs. Single-agent target doses of up to 600 mg have been shown to be tolerable in patients with CLL.

Furthermore, Study M12-630 has shown tolerability of starting doses of venetoclax of up to 1200 mg in combination with chemoimmunotherapy without observation of clinically significant TLS.

The starting dose of venetoclax in this study will be 200 mg. Given that venetoclax will be administered to patients in conjunction with obinutuzumab or rituximab and idasanutlin, which by themselves have a degree of myelosuppression, doses of venetoclax up to the MTD achieved when given as monotherapy may not be tolerable in this combination. Therefore, subsequent dose cohorts will be treated at progressively higher doses, up to a final daily dose of 800 mg if tolerated. The number of cycles of dosing (six 28-day cycles) is designed to provide treatment duration consistent with other therapies for NHL that have been shown to be sufficient to provide durable responses.

The duration of venetoclax dosing, Days 1–10, is designed to provide overlapping exposure with idasanutlin and obinutuzumab or rituximab as well as to reduce possible toxicity of the combination. Furthermore, a safety cohort will be first evaluated with a shorter venetoclax treatment duration, Days 1–5, to ensure the safety and tolerability of

the combination before moving to a Days 1–10 regimen. Extended dosing of venetoclax for up to 1 year in total with obinutuzumab or rituximab and idasanutlin will allow exploration of whether additional activity is observed during the extended (post-induction) dosing period.

#### 3.3.2.4 Rationale for Treatment Duration

In this study, patients with R/R FL or DLBCL will receive six cycles of induction treatment followed by post-induction treatment, with the objective to improve the response to induction therapy, either by converting a PR to a CR, or by eradicating minimal residual disease (MRD) to achieve a molecular response in patients with a clinical CR after induction treatment, thus reducing the relapse risk for responders. In this study, MRD levels will be measured during the post-induction period as an additional means to evaluate the triple combination as post-induction treatment.

Despite recent improvements in therapy for FL, including demonstrated benefit from 2-year rituximab maintenance in patients who responded to first-line immunochemotherapy (Study MO18264), FL is still not considered curable, with a 6-year PFS of 59.2% (Salles et al. 2013). A Phase III study, GAO4753g, investigated GB compared with bendamustine alone in patients with R/R indolent NHL ($n = 396$). Patients in the GB group who had not experienced disease progression at the EOI received obinutuzumab monotherapy every 2 months for up to 2 years. PFS was significantly longer in the GB arm, with a median PFS of 29 versus 14 months (HR: 0.48; 95% CI: 0.35, 0.67; $p < 0.0001$) (Trněný et al. 2016). The data support further investigation of obinutuzumab in combination with new targeted drugs in the setting of induction and maintenance treatment for patients with FL.

Patients with R/R DLBCL who are not suitable for or do not benefit from consolidative autologous transplantation exhibit a poor prognosis. Responses obtained with different rituximab treatment regimens tested in clinical trials (e.g., rituximab in combination with bendamustine, with gemcitabine plus oxaliplatin, or with lenalidomide) have been of short duration, with the longest reported median PFS of approximately 7 months observed in one study of BR (Ohmachi et al. 2013). Thus, 6 months of consolidation treatment, for a total treatment duration of approximately 12 months, is considered to be a reasonable exploratory therapeutic approach in patients with R/R DLBCL with an anticipated positive benefit–risk ratio. On the basis of the complementary mechanism of action between all three study drugs and considering the aggressiveness of R/R DLBCL, this study was designed to investigate the safety and efficacy of the triple combination in the consolidation setting.

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

In DLBCL, the prognostic value of the post-treatment fluorodeoxyglucose (FDG) PET-CT scan has been well documented (Thomas et al. 2010; Vitolo et al. 2010). PET-CT scans have been incorporated in the Lugano 2014 criteria (Cheson et al. 2014) and are

commonly used to assess efficacy in medical practice and clinical trials in lymphoma. More recently, the value of post-induction PET-CT status has been investigated as a prognostic marker for long-term outcome in patients with FL. In the first-line setting, results from a pooled analysis of 246 patients enrolled in three studies and having PET-CT scans available at the end of chemoimmunotherapy showed—with a median follow-up of 55 months—a 4-year PFS in PET-CT–positive and PET-CT–negative patients of 23.2% (95% CI: 11.1%, 37.9%) versus 63.4% (95% CI: 55.9%, 70.0%; $p < 0.001$), respectively, and a 4-year survival rate of 87.2% (95% CI: 71.9%, 94.5%) versus 97.1% (95% CI: 93.2%, 98.8%; $p < 0.0001$), respectively (Trotman et al. 2014).

In the relapsed FL setting, results from a preliminary analysis of the Phase II study BO21003 comparing obinutuzumab versus rituximab monotherapy demonstrated that the post-induction PET-CT status is strongly prognostic of PFS. With a median follow-up of 32.1 months, the risk of disease progression was significantly reduced in PET-CT–negative patients compared with that for the PET-CT–positive patients, regardless of the assessment criteria, either International Harmonization Project criteria (HR, 0.25; 95% CI: 0.191, 0.807; $p = 0.0083$) or European Organization for Research and Treatment of Cancer (EORTC) criteria (HR, 0.39; 95% CI: 0.191, 0.807; $p = 0.0083$) (Kostakoglu et al. 2014).

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

### 3.3.4 Rationale for Biomarker Assessments

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

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

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

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

#### 3.3.4.2 Rationale for p53 and Pharmacodynamic Marker Assessments

The activity of idasanutlin is derived from the disruption of MDM2:p53 protein–protein interaction, thus reducing MDM2-mediated ubiquitination and subsequent degradation of p53. This stabilization and accumulation of p53 confer enhanced function, including transcriptional activity. Therefore, defining cancer cells with respect to their ability to undergo p53 activation is important in achieving the desirable PD effects in vivo (i.e., inhibition of cancer cell growth and apoptosis). Furthermore, MDM2 status is important with regard to the ability to activate p53 because MDM2 is overexpressed in a wide variety of hematologic malignancies, for instance, in approximately 50% of patients with AML (Fenaux et al. 1992; Hu et al. 1992; Wattel et al. 1994). This is believed to result in decreased p53 levels and activity, and p53 function could be restored by MDM2 antagonists. Activated p53 induces or inhibits the expression of multiple genes, some of which are secreted, and may be useful as PD indicators of clinical activity of idasanutlin.

Given as a single agent, idasanutlin demonstrated anti-tumor activity in cultured tumor cells with wild-type tp53. At the same concentrations, it is approximately 300-fold less active in cultured cells with mutated tp53. However, it is possible that not all tp53 mutations may disrupt p53 downstream activity. In NHL, the tp53 mutation rate is less than that of solid tumors and is estimated to be approximately 18% in DLBCL (Ichikawa et al. 1997) and 21% in FL (Møller et al. 1999).

Lymphoma cells from patients will be tested for TP53 mutation, retrospectively, during this study. The data will be used to evaluate the role of TP53 mutation in lymphoma cells and response to treatment with idasanutlin, venetoclax, and obinutuzumab or rituximab.

MDM2 mRNA expression in blood was found to be associated with clinical response in the Phase I study NO21279 in patients with AML treated with RO5045337; however, the association is not sufficiently robust to use MDM2 alone for selection of responsive patients. Multigene transcripts expression algorithm(s) may provide a means of predicting patient response to MDM2 inhibitors. A signature of four genes (*MDM2, BBC3/PUMA, XPC, and CDKN2A*) has been shown to be associated with response to the MDM2-antagonist RO5045337 in nonclinical experiments as well as in the clinical studies NO21279 (RO5045337) and NP28679 (idasanutlin) (Zhong et al. 2015). Further evaluation of this algorithm is ongoing in Phase I studies as well as an ongoing Phase III AML study of idasanutlin. Analysis of this four-gene algorithm in NHL-derived tumor tissue may be associated with patients who are likely to display propensity to have activatable p53.

Additional information for patient-predicted efficacy may be gained from baseline protein expression levels of genes such as, but not limited to, MDM2 and/or p53 from archival material or fresh biopsied lymphoma tumor by immunohistochemistry (IHC) of formalin-fixed, paraffin-embedded (FFPE)-derived tissue and digital pathology protein expression assessment. Indeed, baseline assessment of MDM2 protein expression specifically in malignant cells of interest, here AML leukemic blasts, in Study NP28679 has shown that composite complete remission in AML patients treated with idasanutlin-based therapy was associated with higher levels of MDM2 expression (Reis et al. 2016).

MIC-1, a secreted protein that is strongly induced by p53, can be detected in the blood of mice bearing human tumor xenografts after treatment with doxorubicin, a genotoxic p53 activator (Yang et al. 2003). In Study NO21279 evaluating RO5045337, which included patients with AML and patients in the AML Phase I study NP28679 for idasanutlin, MIC-1 expression was shown to be a useful PD biomarker correlating with exposure. Ongoing evaluation of PD biomarker activity in the aforementioned clinical studies demonstrated treatment-related increases in p53 activity, likely through the activation of *P53* gene targets and induction of apoptosis (Kojima et al. 2005). On the basis of the results from these studies, additional analyses on tumor specimens may be performed as exploratory studies for biomarkers related to p53 and MDM2 activity and the activity of idasanutlin (Ray-Coquard et al. 2012).

#### 3.3.4.3 Rationale for Assessment of Minimal Residual Disease

MRD measurement is an increasingly recognized tool for response assessment in B-cell malignancies. Circulating lymphoma cells and tumor DNA can be detected and quantified at low levels as MRD to assess the degree of response and monitor patients for possible disease recurrence.

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

In this study, MRD will be quantified by circulating lymphoma cells and cell-free circulating-tumor DNA as an exploratory endpoint. MRD assessments will be performed at the EOI to allow for an evaluation of the depth of response, and during post-induction treatment to allow for an evaluation of long-term response or possible disease recurrence.

# 4. MATERIALS AND METHODS

## 4.1 PATIENTS

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

### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (see Appendix 7)
- B-cell lymphoma classified as either of the following:
  - R/R FL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody
  - Relapsed or refractory DLBCL after treatment with at least one prior chemoimmunotherapy regimen that included an anti-CD20 monoclonal antibody in patients who are not eligible for second line combination chemotherapy and autologous stem-cell transplantation, have failed second line combination chemotherapy, or experienced disease progression following autologous stem-cell transplantation
- Histologically documented CD20-positive lymphoma, as determined by a local laboratory
- FDG-avid lymphoma (i.e., PET-positive lymphoma)
- At least one bi-dimensionally measurable lesion (> 1.5 cm in its largest dimension by CT scan or magnetic resonance imaging [MRI])
- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL
  - If the archival tissue is unavailable or unacceptable, a pretreatment core-needle, excisional or incisional tumor biopsy is required. Cytological or fine-needle aspiration samples are not acceptable. Additional details are provided in Section 4.5.6.
  - If a patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, a core-needle biopsy is strongly recommended.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) *or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:*
  - *Women must remain abstinent* or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 18 months after the last dose of study treatment *for those treated with obinutuzumab, idasanutlin,*

*and venetoclax; and for at least 12 months after the last dose of study treatment for those treated with rituximab, idasanutlin, and venetoclax (see Section 5.4.3.1). Women must refrain from donating eggs during this same period.*

  - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
  - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
  - With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 3 months after the last dose of study treatment. Men must refrain from donating sperm during this same period.
  - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study treatment to avoid exposing the embryo.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

### 4.1.2 Exclusion Criteria

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

- Known CD20-negative status at relapse or progression
- Prior allogeneic SCT
- Completion of autologous SCT within 100 days prior to Day 1 of Cycle 1
- Prior standard or investigational anti-cancer therapy as specified below:
  - Radioimmunoconjugate within 12 weeks prior to Day 1 of Cycle 1
  - Monoclonal antibody or antibody–drug conjugate within 4 weeks prior to Day 1 of Cycle 1

  - Radiotherapy, chemotherapy, hormonal therapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1
- Clinically significant toxicity (other than alopecia) from prior therapy that has not resolved to Grade $\leq 2$ (according to NCI CTCAE v4.0) prior to Day 1 of Cycle 1
- Grade 3b FL
- History of transformation of indolent disease to DLBCL (expansion-phase only)

  History of transformation of indolent disease is allowed in the dose escalation phase.
- Central nervous system lymphoma or leptomeningeal infiltration
- Treatment with systemic corticosteroids $> 20$ mg/day, prednisone or equivalent
  - Patients receiving corticosteroids $\leq 20$ mg/day, prednisone or equivalent, for reasons other than lymphoma must be documented to be on a stable dose for at least 4 weeks prior to Day 1 of Cycle 1.
  - If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg/day of prednisone or equivalent may be given for a maximum of 5 days, but all tumor assessments must be completed prior to start of corticosteroid treatment.
- Clinical conditions requiring treatment with oral or parenteral anticoagulants or antiplatelet agents (e.g., chronic daily treatment with aspirin $> 325$ mg/day, clopidogrel, warfarin, systemic low-molecular-weight heparin [LMWH]) unless treatment can be discontinued 7 days (or 5 half-lives) prior to initiation of study treatment (except used as flushes for indwelling catheters)
- Refusal of blood products and/or sensitivity to blood products
- History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies
- Known hypersensitivity or allergy to murine products or any component of the obinutuzumab, rituximab, idasanutlin, or venetoclax formulation
- Infection considered by the investigator to be clinically uncontrolled or poses an unacceptable risk to the patient upon the induction of neutropenia, that is, patients who are or should be on antimicrobial agents for the treatment of active infection such as the following:
  - Fungal infection with visceral involvement, other than mucosal candidiasis, with $< 2$ weeks of appropriate systemic antifungal therapy
  - Bacterial infection with positive cultures within 7 days prior to initiation of study treatment
  - Patients who have received $< 5$ days of appropriate therapeutic antibiotic therapy for an identified infection
  - Neutropenic fever considered infection related within 72 hours prior to initiation of study treatment

- History of symptomatic *C. difficile* infection that required treatment within 1 month prior to dosing

  Upon clinical response to *C. difficile* treatment, the stool consistency and frequency must have returned to normal.

In all cases, the patient should be afebrile and hemodynamically stable for at least 72 hours at the time of study treatment initiation.

Caution should be exercised when considering the use of obinutuzumab or rituximab in patients with a history of recurring or chronic infections.

- Treatment with the following agents within 7 days prior to the first dose of venetoclax and idasanutlin:
  - Strong and moderate CYP3A inhibitors such as fluconazole, ketoconazole, and clarithromycin
  - Moderate CYP3A inducers such as bosentan
  - CYP2C8 substrates such as repaglinide
  - UGT1A3 inhibitor gemfibrozil
  - OATP1B1/3 substrates such as statin drugs
- Treatment with the following agents within 14 days prior to the first doses of venetoclax and idasanutlin
  - Strong CYP3A inducers such as rifampin (also a CYP2C8 inducer) and carbamazepine
- Chronic use of CYP2C8 or OATP1B1/3 substrates
- Consumption of grapefruit, grapefruit products, Seville oranges (including marmalade that contains 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 (e.g., Child-Pugh class B and C)
- Current or history of HBV or HCV infection: positive for hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at screening
  - Patients are eligible if both HBsAg and HBcAb are negative but tested positive for hepatitis B surface antibody (HBsAb) after vaccination.
- Known history of HIV-positive status
  - For patients with unknown HIV status, HIV testing must be performed at screening if not in contradiction with local regulations.
- History of PML
- Vaccination with a live virus vaccine within 28 days prior to Day 1 of Cycle 1

- History of other malignancy that could affect compliance with the protocol or interpretation of results, with the exception of the following:
  - Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer
  - Any previously treated malignancy that has been in remission without treatment for $\geq 2$ years prior to enrollment
- Evidence of any significant, uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm), or uncontrolled irritable bowel disease (i.e., Crohn disease, ulcerative colitis, diverticulosis-associated colitis, and Behçet disease)
- Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by study treatment, such as severe hereditary coagulation disorders or insulin-dependent diabetes mellitus that is not optimally controlled with medical management (e.g., presence of ketoacidosis)
- Major surgical procedure other than for diagnosis within 28 days prior to Day 1 of Cycle 1, or anticipation of a major surgical procedure during the study
- Inadequate hematologic function (unless due to underlying lymphoma), defined as follows:
  - Hemoglobin $< 9$ g/dL
  - ANC $< 1.5 \times 10^9$ cells/L
  - Platelet count $< 75 \times 10^9$ cells/L
- Any of the following abnormal laboratory values (unless due to underlying lymphoma):
  - Calculated creatinine clearance $< 50$ mL/min using the modified Cockcroft-Gault (see Appendix 11)
  - Patients with clinically significant persistent electrolyte abnormalities, such as hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypermagnesemia of Grade $> 1$ according to NCI CTCAE, v4.0

    Treatment for correction of above electrolyte imbalances is permitted during screening to meet eligibility criteria.
  - AST or ALT $> 2.5 \times$ ULN
  - Serum total bilirubin $> 1.5 \times$ ULN (or $> 3 \times$ ULN for patients with Gilbert syndrome)
  - INR or PT $> 1.5 \times$ ULN in the absence of therapeutic anticoagulation
  - PTT or aPTT $> 1.5 \times$ ULN in the absence of a lupus anticoagulant

- Pregnancy or lactation, or plans to become pregnant during the study

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

## 4.2 METHOD OF TREATMENT ASSIGNMENT

This is a Phase Ib/II, open-label, multicenter, non-randomized study of obinutuzumab in combination with idasanutlin and venetoclax in patients with R/R FL and obinutuzumab or rituximab in combination with idasanutlin and venetoclax in patients with R/R DLBCL. Following determination of the MTDs with idasanutlin and venetoclax in combination with obinutuzumab, cohort(s) of patients with DLBCL will be opened to confirm the MTDs of idasanutlin and venetoclax in combination with rituximab. Following determination of the MTDs of idasanutlin and venetoclax in combination with obinutuzumab, cohort(s) of patients with FL will be opened to explore a different regimen (Regimen B, obinutuzumab alone at Cycle 1 and obinutuzumab in combination with idasanutlin and venetoclax at Cycles 2–6). During the dose-escalation phase, patients will be assigned to dosing groups through use of an interactive voice or Web-based response system (IxRS). During the expansion phase, all patients will be assigned to receive the RP2Ds with the selected regimen via IxRS. If eligible, patients will receive maintenance (FL patients) or consolidation (DLBCL patients) treatment (see Sections 3.1.2 and 3.1.3 for details).

Enrollment tracking will be performed through use of the IxRS. Prior to initiation of screening, study site personnel should confirm through the appropriate communication channel that the planned dose-escalation or expansion cohort is open for enrollment. After written informed consent has been obtained and preliminary eligibility has been established, the study site will submit documentation supporting eligibility to the Sponsor and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves a patient for enrollment, a patient number will be assigned and the patient will be enrolled via the IxRS. The Sponsor will communicate to the sites impending closure of screening for a particular disease cohort.

## 4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are obinutuzumab, rituximab, idasanutlin, and venetoclax and will be supplied by the Sponsor.

### 4.3.1 Formulation, Packaging, and Handling

#### 4.3.1.1 Obinutuzumab

Obinutuzumab will be provided as a single-dose, sterile liquid formulation in a 50-mL glass vial containing 1000 mg of obinutuzumab. For information on the formulation and handling of obinutuzumab, see the Obinutuzumab Investigator's Brochure and the pharmacy manual.

#### 4.3.1.2 Rituximab

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

For information on the formulation and handling of rituximab, see the Rituximab IV Oncology Investigator's Brochure and the Rituximab Pharmacy Manual.

#### 4.3.1.3 Idasanutlin

Idasanutlin will be supplied as film-coated tablets. Four different dose strengths of 50 mg (Ro 550-3781/F17), 200 mg (Ro 550-3781/F16), 300 mg (Ro 550-3781/F13), and 400 mg (Ro 550-3781/F14) were developed and optimized for use in clinical studies. For information on the formulation and handling of idasanutlin, see the Idasanutlin Investigator's Brochure.

#### 4.3.1.4 Venetoclax

Venetoclax will be supplied as film-coated tablets. Two different strengths of 50 mg and 100 mg were developed and optimized for the use in clinical studies. For information on the formulation and handling of venetoclax, see the Venetoclax Investigator's Brochure.

### 4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized in Table 1, Table 2, Table 5, and Table 5 (see Section 3.1).

*Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.4.4.*

#### 4.3.2.1 Obinutuzumab

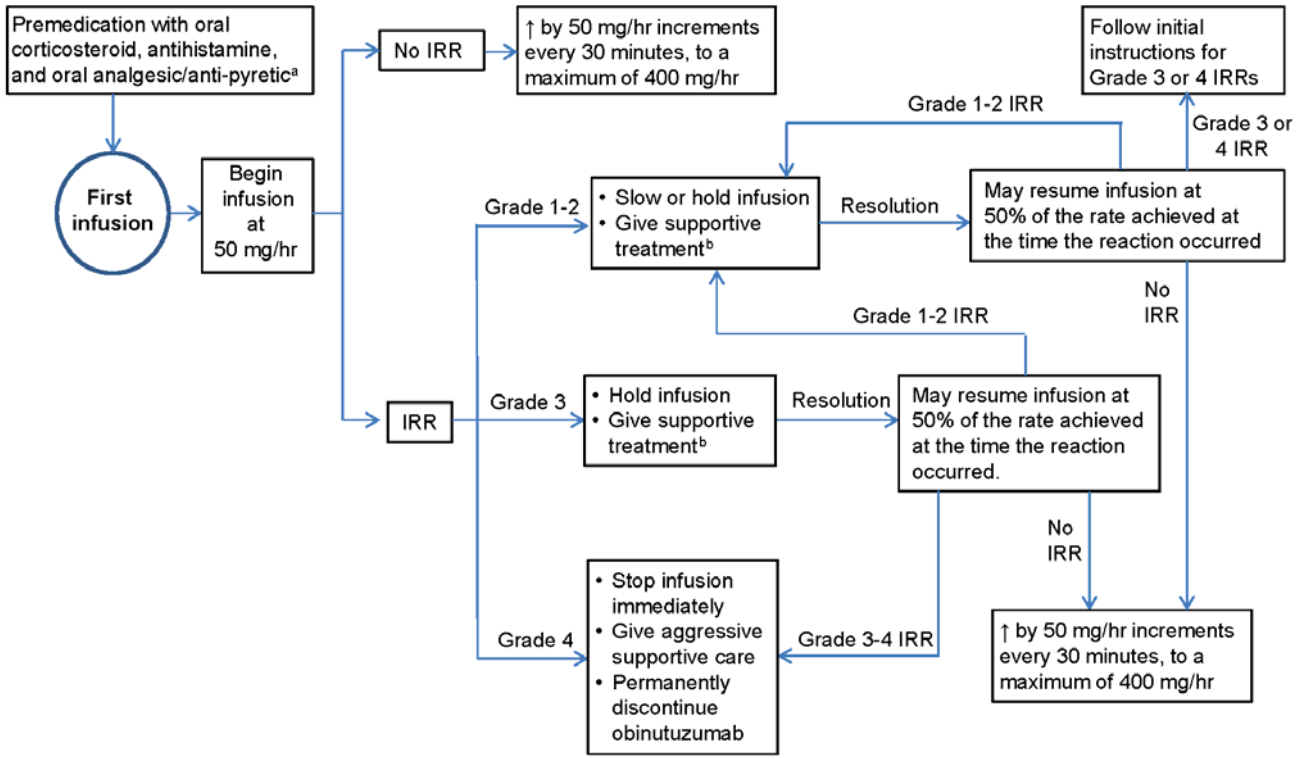
Obinutuzumab will be administered by IV infusion at an absolute (flat) dose of 1000 mg on Days 1, 8, and 15 of the first cycle and on Day 1 of each subsequent cycle during induction treatment, and on Day 1 of every other month (i.e., every 2 months) during maintenance treatment (eligible patients with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

Obinutuzumab should be administered as an IV infusion through a dedicated line in an environment in which full resuscitation facilities are immediately available and under the close supervision of an experienced physician. Obinutuzumab infusions will be administered to patients according to the instructions outlined in Figure 11 and Figure 12. For patients with bulky lymphadenopathy, the infusion may be given extremely slowly over a longer period of time, or the dose may be split and given over more than 1 day.

No dose modification for obinutuzumab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.8.

Premedication with a corticosteroid, antihistamine, and analgesic or antipyretic medication, as outlined in Section 4.3.2.5, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 10.

**Figure 11 Guidelines for Obinutuzumab Infusions: First Infusion**

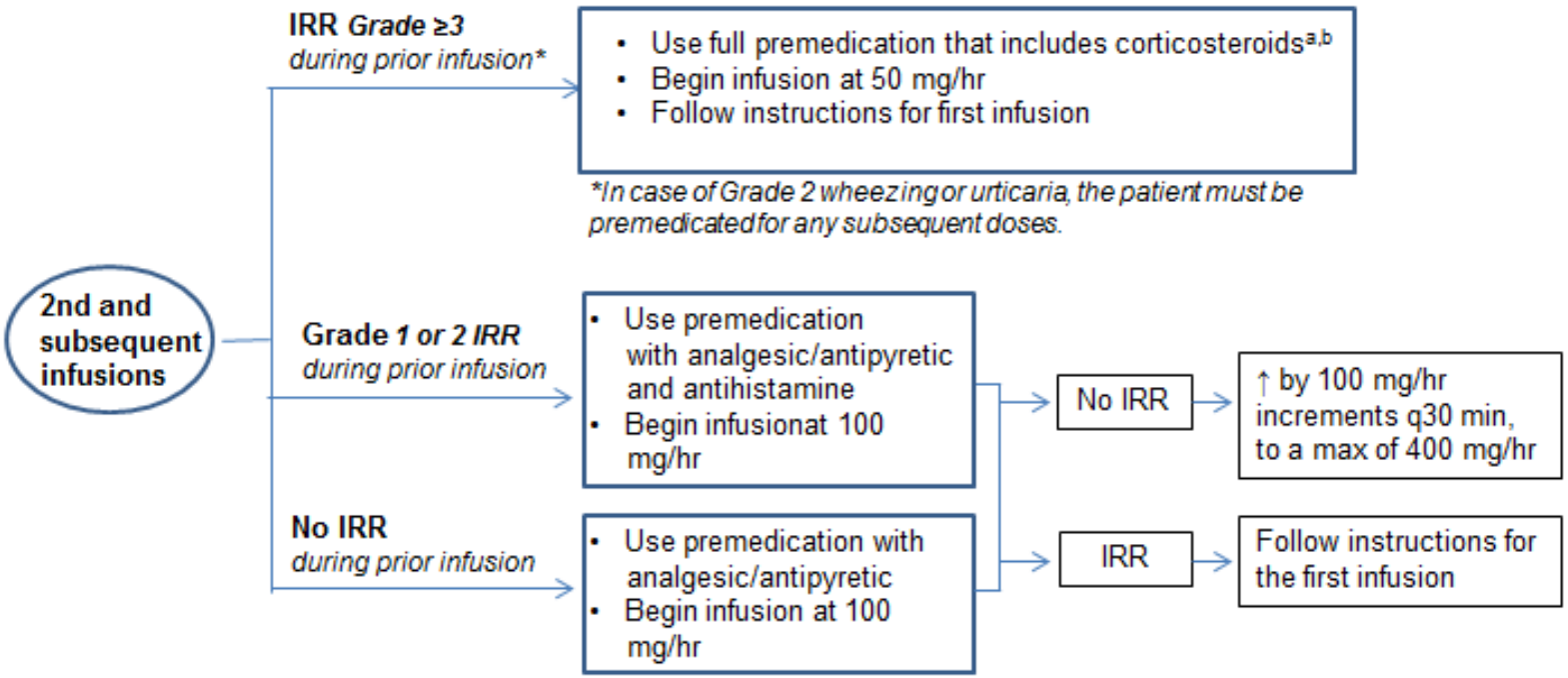



IRR = infusion-related reaction.

[a] All patients should receive full premedication with an oral corticosteroid, antihistamine, and oral analgesic/anti-pyretic medication prior to the first obinutuzumab infusion. Refer to Section 4.3.2.5 for details.

[b] Supportive treatment should include acetaminophen/paracetamol and an antihistamine such as diphenhydramine, if not administered within the previous 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg oral prednisone or equivalent), and/or bronchodilators. For anaphylaxis precautions, see Appendix 10.

**Figure 12 Guidelines for Obinutuzumab Infusions: Second and Subsequent Infusions**




IRR = infusion-related reaction.

[a] Patients should receive full premedication with an oral corticosteroid, antihistamine, and oral analgesic/antipyretic medication prior to the obinutuzumab infusion. Refer to Section 4.3.2.5 for details. In the case of a recurrent Grade 3 IRR, obinutuzumab may be discontinued at the discretion of the investigator, following an individual benefit–risk assessment.

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

#### 4.3.2.2 Rituximab

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

Body surface area (BSA) will be determined at screening and should be used to calculate the dose of rituximab throughout the study unless the patient's weight increases or decreases by $>$ 10% from screening, in which case BSA should be recalculated and used for subsequent dosing. In obese patients (defined as body mass index $\geq$ 30 kg/m$^2$), there is no BSA cap and actual body weight, not adjusted weight, is recommended. Empiric dose adjustment for obese patients may be implemented per institutional guidelines.

The infusion of rituximab may be split over 2 days if the patient is at increased risk for an IRR (high tumor burden or high peripheral lymphocyte count). Administration of rituximab may be continued on the following day, if needed, for patients who experience an adverse event during the rituximab infusion.

If a dose of rituximab is split over 2 days, both infusions must occur with appropriate premedication (see Section 4.3.2.5) and at the first infusion rate (see Table 6).

Rituximab infusions will be administered according to the instructions in Table 6.

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

Rituximab should be administered as a slow IV infusion through a dedicated line. After the end of the first infusion, the IV line or central venous catheter should remain in place for $\geq$ 2 hours in order to administer IV drugs, if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed.

If a patient tolerates the first cycle of study treatment without significant infusion reactions, rituximab may be administered as a rapid infusion (over 60 – 90 minutes) in accordance with local institutional guidelines.

**Table 6 Administration of First and Subsequent Infusions of Rituximab**

| First Infusion (Day 1 of Cycle 1) | Subsequent Infusions |
|---|---|
| • Begin infusion at an initial rate of 50 mg/hr.<br>• If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hr increments every 30 minutes to a maximum of 400 mg/hr.<br>• If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If the reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time when the reaction occurred). | • If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, use full premedication, including 100 mg of prednisone/prednisolone or 80 mg of methylprednisolone or equivalent (until no further IRR occurs); begin infusion at an initial rate of 50 mg/hr; and follow instructions for first infusion.<br>• If the patient tolerated the prior infusion well (defined by an absence of Grade 2 reactions during a final infusion rate of ≥ 100 mg/hr), begin infusion at a rate of 100 mg/hr. If no reaction occurs, increase the infusion rate in 100-mg/hr increments every 30 minutes to a maximum of 400 mg/hr.<br>• If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If the reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time when the reaction occurred). |

IRR = infusion-related reaction.

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

Premedication with a corticosteroid, analgesic/antipyretic, and antihistamine, as outlined in Section 4.3.2.5, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 10.

#### 4.3.2.3 Idasanutlin

Patients will self-administer idasanutlin tablets PO each day according the schedule of activities (see Appendix 1 and Appendix 2) approximately 15 minutes after eating a meal and with water.

On days when idasanutlin, venetoclax, and obinutuzumab are all given, the order of study treatment administration will be idasanutlin followed by venetoclax and obinutuzumab. Idasanutlin should always be given prior to venetoclax if both drugs are to be administered the same day. If vomiting occurs within 15 minutes of taking idasanutlin, 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 in which a QD dose of idasanutlin is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken within 8 hours of the missed dose with food and water. Otherwise, the dose should not be taken. On days when patients are scheduled to have blood samples collected for PK assessments, the time of each dose of idasanutlin will be recorded to the nearest minute.

Idasanutlin must be stored according to labeled storage conditions.

#### 4.3.2.4 Venetoclax

Each once-daily dose of venetoclax (per the dose schedule established during dose escalation) will be taken orally with approximately 240 mL of water within approximately 30 minutes after the completion of breakfast or the 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. The Standard American Heart Association Healthy (Low-Fat) Breakfast includes 1 box cereal (30-40 g), skim milk (240 mL), 1 boiled egg, 1 slice of toast, and margarine (10 g) for approximately 520 Kcal with approximately 17 grams of fat.

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

On days when idasanutlin, venetoclax, and obinutuzumab are all given, the order of study treatment administration will be idasanutlin followed by venetoclax and obinutuzumab. 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. If tablets are not identified, or if any are not intact, no replacement dose is to be given. In cases in which a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible and ensure that the dose is taken with food and water within 8 hours after the scheduled time of the missed dose. Otherwise, the missed dose should not be taken. On days when patients are scheduled to have blood samples collected for PK assessments, the time of each dose of venetoclax will be recorded to the nearest minute.

Venetoclax must be stored according to labeled storage conditions.

#### 4.3.2.5 Premedication

Patients must receive premedication as outlined in Table 7.

## Table 7 Premedication

| Timepoint | Patients Requiring Premedication | Premedication | Administration |
|---|---|---|---|
| Cycle 1, Day 1 | All patients | Oral corticosteroid [a] | Administer ≥ 1 hour prior to obinutuzumab or rituximab infusion. |
| | All patients | • Antihistamine drug [b]<br>• Oral analgesic/anti-pyretic medication [c] | Administer ≥ 30 minutes prior to obinutuzumab or rituximab infusion. |
| Day 1 of the First cycle including venetoclax | All patients | • Appropriate hydration [d] | Administer to 24–48 hours prior to the start of venetoclax and continued for at least 24 hours after the first dose. |
| | | • Administration of an oral agent to reduce uric acid, such as allopurinol 300 mg/day, or rasburicase IV, as judged appropriate by the investigator<br>• Rasburicase IV should be administered (unless medically contraindicated) for those patients with elevated uric acid levels [e] pretreatment | Administer starting 72 hours prior to the first venetoclax dose. If serum uric acid is above ULN administer until normalization of serum uric acid and other laboratory evidence of TLS (e.g., elevated serum LDH levels). [f] |
| | Patients considered at high risk of TLS (see Section 5.1.7.2) | • Hospitalization is required for the initial venetoclax dose. | Refer to Section 5.1.7.2. |

## Table 7 Premedication (cont.)

IRR = infusion-related reaction; TLS = tumor lysis syndrome; ULN = upper limit of normal.

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

[b] For example, 50 mg of diphenhydramine.

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

[d] Fluid intake of approximately 2–3 L/day. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

[e] Defined as a value above the local laboratory's ULN, or above 476 μmol/L (8 mg/dL) if no local laboratory ULN is available.

[f] Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax; otherwise, the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing.

**Table 7 Premedication (cont.)**

| Timepoint | Patients Requiring Premedication | Premedication | Administration |
|---|---|---|---|
| Cycle 1, Days 8 and 15 (for patients receiving obinutuzumab); Cycles 2 and beyond, Day 1 | Patients with no IRR during the previous infusion | • Oral analgesic/anti-pyretic medication [c] | Administer ≥ 30 minutes prior to obinutuzumab or rituximab infusion. For patients receiving rituximab who do not experience any IRR with their previous infusion, premedication may be omitted at the investigator's discretion. |
| | • Patients with Grade 1 or 2 IRR during the previous infusion | • Antihistamine drug [b]<br>• Oral analgesic/anti-pyretic [c] | Administer ≥ 30 minutes prior to obinutuzumab or rituximab infusion. |
| | • Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion<br>• Patients with bulky disease | • Oral corticosteroid [a] | Administer ≥ 1 hour prior to obinutuzumab or rituximab infusion. |
| | | • Antihistamine drug [b]<br>• Oral analgesic/anti-pyretic medication [c] | Administer ≥ 30 minutes prior to obinutuzumab or rituximab infusion. |
| | Patients at high risk of TLS (see Section 5.1.7.2) | • Consider hospitalization if patient is still considered at high risk of TLS (see Section 5.1.7.2), refer to premedication as defined for Cycle 1. | Refer to Section 5.1.7.2. |
| Cycles 1 to 6 | All patients receiving idasanutlin | • Second-generation anti-emetic treatments, such as palonosetron, ondansetron, or granisetron | Administer per individual drug prescribing information. |
| Cycles 1 to 6 | All patients | • No premedication for diarrhea | Not applicable |
| | Patients with previous episode of Grade ≥ 3 | • Loperamide 4 mg orally | Loading dose 30 minutes before first administration of study drug. |

## Table 7 Premedication (cont.)

IRR = infusion-related reaction; TLS = tumor lysis syndrome; ULN = upper limit of normal.

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

[b] For example, 50 mg of diphenhydramine.

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

[d] Fluid intake of approximately 2–3 L/day. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

[e] Defined as a value above the local laboratory's ULN, or above 476 μmol/L if no local laboratory ULN is available.

[f] Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax; otherwise, the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing.

### 4.3.3 Investigational Medicinal Product Accountability

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

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

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

### 4.3.4 Post-Trial Access to Obinutuzumab, Rituximab, Idasanutlin, and Venetoclax

Currently, the Sponsor does not have any plans to provide obinutuzumab, rituximab, idasanutlin, venetoclax, or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing obinutuzumab, rituximab, idasanutlin, and venetoclax in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

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

## 4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 14 days prior to the screening period to the visit at the EOI or at the end of post-induction treatment, whichever occurs later. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

### 4.4.1 Permitted Therapy

Premedication is permitted as described in Section 4.3.2.5.

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

Hematopoietic growth factors are allowed in *all study* phase*s* if clinically indicated and used in accordance with the prescribing information. *G-CSF may be used in the DLT period (Cycles 1 and 2) to treat Grade ≥ 3 neutropenia, but is not allowed as prophylaxis. Outside of the DLT observation window during the dose-escalation phase and during the expansion phase,* G-CSF may be administered in each cycle of therapy

as primary prophylaxis for neutropenia, according to the American Society of Clinical Oncology (ASCO), EORTC, and European Society for Medical Oncology (ESMO) guidelines (Smith et al. 2006) or according to each site's institutional standards.

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

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

### 4.4.2 Prohibited and Cautionary Therapy

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

- Any anti-cancer therapy, approved or investigational, other than intrathecal central nervous system prophylaxis
- Hormonal therapy other than contraceptives, stable hormone-replacement therapy, or megestrol acetate
- Biologic agents other than hematopoietic growth factors (as described in Section 4.4.1)
- Vaccination with live vaccines is not recommended during treatment with obinutuzumab or rituximab and until B-cell recovery

MDM2 antagonists were shown in vitro to affect all types of hematopoietic progenitors, including megakaryocytic differentiation. They inhibit both early and late stages of megakaryopoiesis, including ploidization and proplatelet formation (Mahfoudhi et al. 2016). As a consequence, the effect on early progenitors might induce long-lasting thrombocytopenia in vivo.

Therefore, because of the potential severity and duration of thrombocytopenia induced by study treatment, patients in clinical need for chronic treatment with oral or parenteral anticoagulant/antiplatelet agents (e.g., warfarin, chronic daily treatment with aspirin [$>$ 325 mg/day], clopidogrel, dabigatran, apixaban, rivaroxaban, systemic LMWH, or subcutaneous anticoagulant prophylaxis) are excluded from this study. For patients considered eligible for the study because they are able to tolerate interruption of anticoagulant or antiplatelet treatment, these agents must be discontinued 7 days (or 5 half-lives, whichever is shorter) prior to initiating study treatment (except used as flushes for indwelling catheters). After the study treatment completion or discontinuation visit, treatment with anticoagulant/antiplatelet agents may be re-initiated for patients with transfusion-independent adequate platelet levels as clinically indicated.

Idasanutlin is metabolized mainly by multiple pathways such as CYP3A, CYP2C8, and UGT (UDP glucuronosyltransferase) enzymes. Due to the fact that idasanutlin PK exposure is only minimally changed during treatment with a strong CYP3A inhibitor posaconazole as summarized in Section 1.3.2.1, it is not a sensitive CYP3A or CYP2C8

substrate and thus its metabolism may only be affected by concomitant CYP3A or CYP2C8 inducers. Venetoclax is metabolized by CYP3A4 and CYP3A5 enzymes and is a P-glycoprotein and BRCP substrate; metabolism may be affected by concomitant CYP3A inhibitors and inducers, or P-glycoprotein inhibitors. Idasanutlin M4 metabolite and venetoclax are organic anion-transporting polypeptide (OATP)-1B1/3 transporter inhibitors that may affect concomitant OATP1B1/3 substrates. Idasanutlin inhibits CYP2C8 metabolism, which may affect concomitant CYP2C8 substrates. Venetoclax inhibits P-glycoprotein and BCRP, which may affect concomitant P-glycoprotein and BCRP substrates. Thus, in order to prevent undesirable DDIs during the study, the use of any of the medications listed in Table 8 (CYP2C8 substrates) and Table 10 (OATP1B1/3 substrates) is prohibited, while the use of any of the medications listed in Table 9 (strong and moderate CYP3A inhibitors and inducers) is either prohibited within the DLT evaluation window (first two cycles in the escalation phase) or allowed after the DLT evaluation window after being washed out in sufficient duration (for inhibitors) or concomitant use with caution (for inducers). Note that gemfibrozil is also a potent UGT1A3 inhibitor that will be excluded from use in this study. Medications listed in Table 11 should be used with caution because of potential DDIs with venetoclax.

The UGT1A3 inhibitor gemfibrozil, the CYP2C8 substrates listed in Table 8, the CYP3A inhibitors and moderate CYP3A inducers listed in Table 9, and the OATP1B1/3 substrates listed in Table 10 must be discontinued 7 days prior to start of study treatment. Strong CYP3A inducers listed in Table 9 must be discontinued 14 days prior to the start of study treatment.

### Table 8 Prohibited CYP2C8 Substrates

| Substrates |
|---|
| Amiodarone |
| Amodiaquine |
| Cerivastatin |
| Chloroquine |
| Ibuprofen |
| Lovastatin |
| Montelukast |
| Paclitaxel |
| Pioglitazone |
| Repaglinide |
| Rosiglitazone |
| Simvastatin |
| Toresamide |

## Table 9 Examples of Strong and Moderate CYP3A Inhibitors and Inducers

| CYP3A Inhibitors | | CYP3A Inducers | |
|---|---|---|---|
| Strong [a] | Moderate [b] | Strong [c] | Moderate [c] |
| boceprevir | aprepitant | carbamazepine | bosentan |
| clarithromycin | cimetidine | enzalutamine | efavirenz |
| cobicistat | ciprofloxacin | mitotane | etravirine |
| conivaptan | clotrimazole | phenytoin | modafinil |
| | | rifampin | |
| danoprevir/ritonavir | crizotinib [d] | St. John's wort | |
| diltiazem | cyclosporine [d] | | |
| elvitegravir/ritonavir | dronedarone | | |
| idelalisib [d] | erythromycin | | |
| indinavir | fluconazole | | |
| itraconazole | fluvoxamine | | |
| ketoconazole | imatinib [d] | | |
| lopinavir/ritonavir | tofisopam | | |
| nefazodone | verapamil | | |
| nelfinavir | | | |
| ritonavir | | | |
| paritaprevir/ritonavir combinations | | | |
| posaconazole | | | |
| saquinavir/ritonavir | | | |
| telaprevir | | | |
| tipranavir/ritonavir | | | |
| troleandomycin | | | |
| voriconazole | | | |

[a] Concomitant use of venetoclax with strong CYP3A inhibitors is to be avoided to prevent venetoclax exposure elevation with potentially increased toxicities; use an alternative medication that is not an inhibitor. If must be used medically, they are allowed during the study only if the patient has completed the DLT evaluation window (if patient is in a dose escalation cohort) and venetoclax is withheld in that cycle. After discontinuation of the strong CYP3A inhibitor, wait for 7 days before restarting venetoclax treatment. As obinutuzumab and idasanutlin (not a sensitive CYP3A substrate with regard to CYP3A inhibition) PK exposures are not expected to be affected from CYP3A inhibition, their dosing schedules should continue in 28-d cycles if venetoclax has to be withheld in the study.

[b] Concomitant use of venetoclax with moderate CYP3A inhibitors is to be avoided to prevent venetoclax exposure elevation with potentially increased toxicities; use an alternative medication that is not an inhibitor. If must be used medically, they are allowed during the study only if the patient has completed the DLT evaluation window (if patient is in a dose escalation cohort) and a 50% dose reduction for venetoclax is implemented in that cycle. After discontinuation of the moderate CYP3A inhibitor, wait for 3 days before increasing venetoclax back to the initial dose

## Table 9 Examples of Strong and Moderate CYP3A Inhibitors and Inducers (cont.)

[c] Concomitant use of venetoclax and idasanutlin with strong or moderate CYP3A inducers is to be avoided to prevent venetoclax and idasanutlin exposure loss compromising efficacy; consider alternative medications. If the patient requires use of these medications, use with caution and contact Roche Medical Monitor (refer to Section 5.4.1) for guidance. The inducers are allowed during the study only if the patient has completed the DLT evaluation window (if patient is in a dose escalation cohort).

[d] These are anti-cancer agents; consult with the Medical Monitor before use.

## Table 10 Prohibited OATP1B1/3 Substrates

| OATP1B1/3 Substrates [a] |
|---|
| Asunaprevir |
| Atorvastatin |
| Atrasentan |
| Bosentan |
| Cerivastatin |
| Danoprevir |
| Docetaxel |
| Ezetimibe |
| Fexofenadine |
| Fluvastatin |
| Glyburide |
| Irinotecan |
| Nateglinide |
| Olmesartan |
| Paclitaxel |
| Pitavastatin |
| Pravastatin |
| Repaglinide |
| Rifampin |
| Rosuvastatin |
| Simvastatin acid |
| Telmisartan |
| Valsartan |

[a] OATP1B1/3 substrates with $t_{1/2}$ shorter than 1 day are allowed, except during idasanutlin treatment and for 72 hours after the last dose of idasanutlin.

**Table 11 Cautionary Medications for Venetoclax**

| CYP3A | | P-Glycoprotein | |
|---|---|---|---|
| Weak Inhibitors | Weak Inducers | Substrates | Inhibitors |
| alprazolam<br>amiodarone<br>amlodipine<br>bicalutamide [a]<br>chlorzoxazone<br>cilostazol<br>cimetidine<br>fluoxetine<br>fosaprepitant<br>ginkgo<br>goldenseal<br>isoniazid<br>istradefylline<br>ivacaftor<br>lomitapide<br>nilotinib [a]<br>oral contraceptives<br>pazopanib [a]<br>ranitidine<br>ranolazine<br>tacrolimus<br>tipranavir/ritonavir<br>ticagrelor<br>zileuton | amprenavir<br>aprepitant<br>armodafinil<br>clobazamechinacea<br>prednisone<br>rufinamide<br>vemurafenib [a] | aliskiren<br>ambrisentan<br>colchicine<br>dabigatran etexilate<br>digoxin<br>everolimus [a]<br>fexofenadine<br>lapatinib [a]<br>loperamide<br>maraviroc<br>nilotinib [a]<br>ranolazine<br>saxagliptin<br>sirolimus [a]<br>sitagliptin<br>talinolol<br>tolvaptan<br>topotecan [a] | amiodarone<br>azithromycin<br>captopril<br>carvedilol<br>dronedarone<br>felodipine<br>propafenone<br>quinidine<br>ranolazine<br>ticagrelor |

| BCRP | |
|---|---|
| Substrates | Inhibitors |
| methotrexate [a]<br>mitoxantrone [a]<br>lapatinib [a]<br>sulfasalazine<br>topotecan [a] | geftinib [a] |

[a] These are anti-cancer agents; consult with the Medical Monitor before use.

The lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication

should be inhibited by the above rationale. In addition, the investigator should contact the Medical Monitor if questions arise regarding any medications not listed above.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

### 4.4.3 Additional Restrictions

Use of the following foods is prohibited during the study and for at least 3 days before **initiation of study treatment:**

- Grapefruit
- Grapefruit juice
- Products that contain grapefruit
- Seville oranges (including marmalade that contains Seville oranges)
- Star fruit

## 4.5 STUDY ASSESSMENTS

Please see Appendix 1 and Appendix 2 for the schedules of activities performed during the study.

### 4.5.1 Informed Consent Forms and Screening Log

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

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

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

Study treatment should be initiated within 28 days after the Informed Consent Form has been signed. Those patients who fail screening based on longer waiting times for certain results or due to study technical reasons (such as cohort on hold) can be rescreened once at a later date if they were deemed eligible before the screen failure. The decision to rescreen individual patients will be made jointly by the Roche Medical Monitor and the investigator and any other person the investigator or Medical Monitor considers necessary to assist with this decision. Any such decision and the reasons for

it will be clearly documented. Any out-of-window assessments need to be repeated and undergo a complete review by the Roche Medical Monitor.

### 4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, and alcohol and drug abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to the screening period will be recorded.

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

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

- Date of initial diagnosis
- ECOG performance status (see Appendix 7)
- Ann Arbor staging (see Appendix 8)
- For patients with FL: FLIPI and FLIPI2 (see Appendix 9)
- For patients with DLBCL: IPI (see Appendix 9)
- B symptoms (unexplained fever $>$38°C, night sweats, and unexplained weight loss $>$10% of body weight over 6 months)
- Previous lines of anti-lymphoma treatment as well as response to prior therapy, date of disease progression in relation to start date of prior treatment, and date of last dose of prior treatment

### 4.5.3 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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

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

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

*In cases that physical examinations reveal visible manifestations of lymphoma or of toxicities (skin involvement, rashes, etc.), additional assessments and measures (such as pictures, measurements) could be undertaken upon additional patient consent.*

### 4.5.4 Vital Signs

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

### 4.5.5 Tumor and Response Evaluations

All evaluable or measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the IRC and the investigator on the basis of PET and CT scans using the Lugano 2014 criteria (see Appendix 4), taking into account results of bone marrow assessments for patients with bone marrow involvement at screening.

In this study, the Lugano 2014 criteria for a PET-CT–based CR have been slightly modified to require normal bone marrow for patients with bone marrow involvement at screening (see Appendix 4). Additionally, designation of a PET-CT–based PR requires that CT-based response criteria for a CR or PR be met in addition to the PET-CT–based response criteria for PR (see Appendix 4).

#### 4.5.5.1 Radiographic Assessments

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

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

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

If contrast is medically contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans of the chest, abdomen, and pelvis (and neck, if clinically indicated) and a non-contrast CT scan of the chest may be performed. If MRI scans

cannot be obtained, CT scans without contrast are permitted as long as these allow consistent and precise measurement of the targeted lesions during the study treatment period.

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

A full tumor assessment, including radiographic assessment, must be performed any time disease progression or relapse is suspected.

Additional details regarding imaging procedures will be provided in the imaging manual.

#### 4.5.5.2 Bone Marrow Assessments

Bone marrow assessments, consisting of bone marrow biopsy and aspiration, are required at screening for staging purposes in all patients and should be performed within approximately 3 months prior to Day 1 of Cycle 1.

For patients with bone marrow involvement at screening, a repeat assessment will be performed if there is radiologic evidence of a complete response or if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression) (see Appendix 1 for details).

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

### 4.5.6 Laboratory, Biomarker, and Other Biological Samples

#### Local Laboratory Assessments

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

- Hematology: hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum or plasma): sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, amylase, lipase, LDH, and uric acid
- $\beta_2$ microglobulin
- Coagulation: INR, aPTT (or PTT), and PT
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening (within 7 days of Day 1 of Cycle 1). Because of the suspected effect idasanutlin on embryo-fetal development, monthly pregnancy testing is strongly recommended for women of childbearing potential.

- Viral serology

  Hepatitis B testing includes HBsAg and total HBcAb.

  Hepatitis C testing includes HCV antibody.
- Quantitative immunoglobulins: IgA, IgG, and IgM
- Bone marrow assessment

### Central Laboratory Assessments

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

- Serum samples for obinutuzumab PK analysis using a validated assay
- Serum samples for rituximab PK analysis using a validated assay
- Plasma samples for idasanutlin (and metabolites) PK analysis using a validated assay
- Plasma samples for venetoclax (and metabolites) PK analysis using a validated assay
- Tumor tissue samples and the corresponding pathology report collected at baseline for retrospective central confirmation of the diagnosis of FL or DLBCL and for exploratory research on biomarkers (see Table 12)

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

  FFPE tissue blocks are preferred over slides. Tissue blocks that are not formalin fixed will be accepted in countries that use a fixative other than paraformaldehyde, but information on the type of fixative should be included. If a tissue block is not available, 17–22 serial, freshly cut, unstained slides accompanied by a punch biopsy may be sent. A tumor block or punch biopsy is required for construction of a tissue microarray. If fewer than 17–22 unstained, serial slides are available, the study site should consult the Sponsor (or delegate) regarding the acceptability of a fewer number of slides.

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

  If the patient received anti-lymphoma treatment between the time of the most recent available biopsy and initiation of study treatment, a core-needle biopsy is strongly recommended.

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

  Analysis methods will be detailed in the Biomarker Analysis Plan.

- Tumor biopsy samples obtained at the time of progression (unless no adequate tumor site is accessible) for exploratory research on biomarkers (see Table 12)

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 12.

**Table 12 Proposed Non-Inherited Biomarkers for Exploratory Analysis**

| Sample Type | Timing | Proposed Biomarkers |
|---|---|---|
| Serum | Baseline and subsequent timepoints during treatment | • MIC-1 |
| Blood for MRD | Baseline and subsequent timepoints during and after treatment | • Circulating lymphoma cells<br>• Cell-free circulating-tumor DNA |
| Blood | Baseline and subsequent timepoints during and after treatment | • Lymphocyte immunophenotyping, including B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and NK cell counts (CD16 and CD56) |
| Archival or fresh tumor tissue | Prior to study (archival) or baseline (fresh)<br>Fresh biopsy at time of progression | • mRNA (DLBCL only): cell-of-origin subtype (ABC vs. GCB)<br>• Lymphoma-related genetic changes (DNA) and gene expression (mRNA)<br>• Identification of lymphoma clone identifier (B cell–receptor sequence) for subsequent MRD assessment in blood<br>• TP53 mutation status<br>• IHC (ex p53, MDM2, PUMA, BCL2, and MYC)<br>• mRNA expression for MDM2, XPC, BBC3 (PUMA,) and CDKN2A (p16/INK4A, ARF,) BCL-2, MYC (myc in DLBCL only)<br>• Fluorescence in situ hybridization for *MYC* and *BCL-2* gene amplification |

ABC = activated B cell–like (subgroup); DLBCL = diffuse large B-cell lymphoma; GCB = germinal-center B cell–like (subgroup); ICH = immunohistochemistry; MRD = minimal residual disease; NK = natural killer; PBMC = peripheral blood mononuclear cell.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her remaining samples to be stored for optional exploratory research (Section 4.5.9), biological samples will be destroyed

when the final Clinical Study Report (CSR) has been completed, with the following exception:

- Plasma or serum samples collected for PK analysis will be destroyed no later than 5 years after the final CSR has been completed.
- Blood, plasma, serum, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis, including data on germ-line mutations, will be subject to the confidentiality standards described in Section 8.4.

### 4.5.7 Electrocardiograms

Resting 12-lead ECG recordings will be obtained in triplicate at specified timepoints, as outlined in the schedule of activities (see Appendix 1 and Appendix 2), and may be obtained at unscheduled timepoints as clinically indicated. ECGs for each patient should be obtained using the same machine wherever possible. All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and under no conditions while the patient is receiving premedication or an IV infusion of study drug. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of a patient's permanent study file at the site. The following should be recorded on the appropriate eCRF: ECG abnormality (including waveform); heart rate; PQ, PR, RR, and QRS intervals; and QT interval and corrected QTcF interval based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

If at a particular post-dose timepoint the mean QTcF is $>$500 ms and/or 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia, etc.) and provide this information on the eCRF. In

the event a patient presents with an episode of Grade ≥2 supraventricular arrhythmia (e.g., atrial fibrillation, atrial flutter, sinus tachycardia), an unscheduled ECG should be reported. Standard-of-care treatment may be instituted at the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled idasanutlin PK sample should be obtained.

ECG sampling assessment windows are as follows:

- Pre-dose: within 2 hours prior to idasanutlin dosing
- Post-dose: 6 hours after idasanutlin dose (±5%; equal to 18 minutes) or after the end of obinutuzumab or rituximab infusion, whichever occurs later

### 4.5.8 Multigated Acquisition Scan or Echocardiogram

Multigated acquisition (MUGA) scans will be obtained prior to treatment (see Appendix 1 and Appendix 2). Echocardiogram is to be used if MUGA is not available. Any clinical significant changes in cardiac function are to be reported within 7 days.

### 4.5.9 Samples for Research Biosample Repository

#### 4.5.9.1 Overview of the Research Biosample Repository

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

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

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

#### 4.5.9.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted

approval for RBR sampling, this section of the protocol (Section 4.5.9) will not be applicable at that site.

#### 4.5.9.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to obinutuzumab, rituximab, idasanutlin, venetoclax, FL, DLBCL, or other types of cancer:

- Remaining tumor tissue samples (except for remaining blocks, which will be returned to the sites)
- Blood for serum
- Remaining peripheral blood

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germ-line mutations, somatic mutations via whole genome sequencing (WGS), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

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

#### 4.5.9.4 Confidentiality

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

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

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

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

#### 4.5.9.5 Consent to Participate in the Research Biosample Repository

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

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

#### 4.5.9.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. *If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:*

*global_rcr-withdrawal@roche.com*

*A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.*

#### 4.5.9.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

## 4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

### 4.6.1 Patient Discontinuation

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

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

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

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

### 4.6.2 Study Treatment Discontinuation

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

- A DLT during the DLT window in patients enrolled in the dose-escalation phase
- Anaphylaxis, acute respiratory distress, or Grade 4 IRR

  If a Grade 3 IRR is recurrent during the second and subsequent cycles, study treatment may be discontinued at the discretion of the investigator, following an individual benefit–risk assessment.
- Any adverse event that leads to a delay of more than 21 days in the start of the next treatment cycle

- Any hematologic adverse event that meets criteria for permanent discontinuation according to the guidelines provided in Section 5.1.8
- Hy's Law cases
- Grade $\geq$3 non-hematologic adverse event that has a reasonable possibility of being related to study treatment and either is life threatening or does not resolve to Grade $<$2 within 21 days
- Disease progression
- Pregnancy

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

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

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

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

### 4.6.3 Study and Site Discontinuation

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

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

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for GCP
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

# 5. ASSESSMENT OF SAFETY

## 5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with study treatment components in completed and ongoing studies. The anticipated important safety risks of IMPs in this study (i.e., obinutuzumab, rituximab, idasanutlin, and venetoclax) are outlined below. Please refer to the Obinutuzumab, Rituximab, Idasanutlin, and Venetoclax Investigator's Brochures for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this trial. Eligibility criteria have been designed to exclude patients at higher risk of toxicities (see Section 4.1). In addition, patients will undergo adequate safety monitoring during the study, as described in this section and in Section 4.5. Guidelines for managing adverse events, including criteria for dosage modification and treatment delays or discontinuation, are provided in Section 5.1.8.

### 5.1.1 Risks Associated with Obinutuzumab

As of 4 July 2016, the following adverse events are considered to be important risks associated with obinutuzumab: IRRs, TLS, neutropenia (including prolonged and late-onset neutropenia), prolonged B-cell depletion, thrombocytopenia (including acute thrombocytopenia), infections (including PML and HBV reactivation), impaired immunization response, worsening of preexisting cardiac conditions, GI perforation, immunogenicity, and second malignancies. These events, with the exception of prolonged B-cell depletion, immunogenicity, and second malignancies, are described below.

#### 5.1.1.1 Infusion-Related Reactions

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

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

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

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

Guidelines for medical management of IRRs and anaphylaxis are provided in Section 4.3.2.1 and Appendix 10.

#### 5.1.1.2 Tumor Lysis Syndrome

TLS, including fatal events, has been reported with obinutuzumab administration. Patients at risk of TLS (e.g., because of bulky disease or renal insufficiency) should receive adequate hydration and premedication with allopurinol or an alternative uricostatic agent as indicated in Section 4.3.2.5 (see Table 8). Additional guidelines for management of TLS in this study are provided in Section 5.1.6.

#### 5.1.1.3 Neutropenia

Grade 3 or 4 neutropenia, including febrile neutropenia, has been reported with obinutuzumab administration. Neutropenia resolved spontaneously or with use of hematopoietic growth factors. Patients who experience Grade 3 or 4 neutropenia should be closely monitored until neutrophil values return to at least Grade 2. Cases of late-onset neutropenia (ANC $<1000$ cells/μL occurring $\geq 28$ days after obinutuzumab treatment has been completed or stopped) or prolonged neutropenia (ANC $<1000$ cells/μL) that does not resolve after 28 days without obinutuzumab treatment have also been reported. Prophylactic treatment with antibiotics should be administered as per standard practice. The use of G-CSF is allowed for treatment of neutropenia in this study. Guidelines for *treatment and* primary prophylaxis with G-CSF are provided in Section 4.4.1.

#### 5.1.1.4 Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. In patients with CLL exposed to obinutuzumab, fatal hemorrhagic events have also been reported during Cycle 1. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients receiving concomitant medication that could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants) may be at greater risk of bleeding and will not be included in the study. Patients should be closely monitored for thrombocytopenia, especially during the first cycle. For patients who experience thrombocytopenia, regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) may be performed at the discretion of the treating physician, according to institutional practice.

#### 5.1.1.5 Infections

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

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

Reactivation of hepatitis B in patients with chronic hepatitis (HBsAg positive) with evidence of prior hepatitis B exposure, or in patients who are carriers (HBsAg negative and HBcAb positive) has been reported with other anti-CD20 antibodies. The risk is increased particularly when anti-CD20 antibodies are administered with immunosuppressive therapies, such as steroids or chemotherapy. Particular attention should be given to patients who have previously received highly immunosuppressive treatment, such as high-dose chemotherapy and SCT. Patients positive for HBsAg and HBcAb are not eligible for this study.

John Cunningham (JC) viral infection resulting in PML has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patients presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary, depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs or symptoms regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA). Additional guidelines for medical management of PML in this study are provided in Table 19.

#### 5.1.1.6 Immunizations

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

#### 5.1.1.7 Worsening of Preexisting Cardiac Condition

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

#### 5.1.1.8 Gastrointestinal Perforation

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

### 5.1.2 Risks Associated with Rituximab

The following adverse events are considered to be important risks associated or potentially associated with rituximab: IRRs, infections (including severe infections), PML, hepatitis B reactivation, neutropenia (including prolonged neutropenia), TLS, impaired immunization response, severe skin reactions (Stevens-Johnson syndrome/toxic epidermal necrolysis), and GI perforation. Details for these risks are provided below; refer to the Rituximab Investigator's Brochure for full information.

#### 5.1.2.1 Infusion-Related Reactions

Acute IRRs are very common in patients receiving rituximab (occurring in $\geq$ 10% of patients) based on clinical trial experience. However, serious IRRs are uncommonly reported (occurring in $\geq$ 1 of 1,000 and $<$ 1 of 100 patients) and are rarely fatal (occurring in $\geq$ 1 of 10,000 and $<$ 1 of 1,000 patients). Most IRRs occur with the first administration of rituximab. Most IRRs are mild to moderate in severity (Grade 1/2) and can be managed by slowing or stopping the rituximab infusion. IRRs can be severe and in rare cases can result in death. Rituximab-induced IRRs consist of a cluster of symptoms and signs occurring during or within 24 hours of a rituximab infusion, which may be related to cytokine release and/or other chemical mediators, and these acute IRRs overlap with "cytokine release syndrome." Anaphylactic and other hypersensitivity reactions have been reported following rituximab administration, and clinical manifestations of these reactions are similar to cytokine release syndrome. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the rituximab infusion.

#### 5.1.2.2 Infections (Including Serious Infections)

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following completion of rituximab-based therapy.

#### 5.1.2.3 Hepatitis B Reactivation

Reactivation of hepatitis B ranges from asymptomatic reactivations (detected by changes in laboratory parameters only) to fulminant liver failure and death. Patients with chronic hepatitis B (HBsAg positive) viral infection are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg negative and anti-HBcAb positive) are at a lower risk for reactivation. Patients who demonstrate evidence of reactivation while receiving an appropriate anti-viral therapy will be discontinued from study treatment.

#### 5.1.2.4 Progressive Multifocal Leukoencephalopathy

Rare cases of PML have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications (Goldberg et al. 2002; Calabrese et al. 2007; Carson and Bennett 2009). In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with rituximab is rare, but it should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic SCT. Most cases of PML were diagnosed within 12 months of the patients' last infusion of rituximab.

#### 5.1.2.5 Neutropenia (Including Prolonged Neutropenia)

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

#### 5.1.2.6 Tumor Lysis Syndrome

Patients treated with rituximab may be at risk for TLS. Severe tumor TLS is very rare in patients receiving rituximab (occurring in < 1 of 10,000 patients), based on postmarketing experience. Signs and symptoms (e.g., hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphatemia, acute renal failure, and elevated LDH) that are consistent with TLS have been reported to occur after the first rituximab IV infusion in patients with high numbers of circulating malignant lymphocytes. A high number of circulating malignant cells (≥ 25,000/$mm^3$) or high tumor burden confers a greater risk of TLS. For patients with evidence of TLS, rituximab should be discontinued, and the patient should be treated as clinically indicated.

#### 5.1.2.7 Impaired Immunization Response

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

#### 5.1.2.8 Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

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

#### 5.1.2.9 Gastrointestinal Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In postmarketing reports of rituximab, the mean time to documented GI perforation was 6 days (range: 1–77 days) in patients with NHL.

### 5.1.3 Risks Associated with Idasanutlin

Information related to idasanutlin-associated risks is based mainly on review of data from Phase I experience in patients with solid tumors and AML (Studies NP27872, NP28902, and NP28679, respectively) as described in the Idasanutlin Investigator's Brochure. In Study NP27872 and NP28902, 160 patients with advanced malignancies (excluding leukemia) have received idasanutlin in the Phase I, entry-into-human, dose-escalation study NP27872 (99 patients) and in the Phase I DDI and relative bioavailability study NP28902 (61 patients). Study BH29812 (idasanutlin plus obinutuzumab in R/R FL and DLBCL) had enrolled 1 patient as of 1 May 2016.

Many of the toxicities experienced by patients with solid tumors appear to be manageable with appropriate prophylaxis, supportive therapies, and/or reversible with discontinuation of idasanutlin. Identified risks include GI disorders (diarrhea, nausea, and vomiting), myelosuppression (thrombocytopenia, neutropenia, and anemia), TLS, infectious complications, and electrolyte abnormalities. Potential risks include coagulation abnormalities and liver function test abnormalities.

Please refer to the current version of the Idasanutlin Investigator's Brochure for additional information on the identified and potential risks.

#### 5.1.3.1 Gastrointestinal Disorders

The adverse GI events in the Phase I idasanutlin studies include primarily diarrhea, nausea, vomiting, and anorexia. Diarrhea is the most common adverse event observed across treatment groups and indications. It has been reported in a large majority of patients treated with idasanutlin and rarely presented as severe. Nausea and vomiting have also been reported during clinical experience with idasanutlin. Clinical monitoring for potential complications is required. Patients who develop GI disorders should have other or concomitant causes ruled out. Appropriate event management and prophylaxis should be considered.

#### 5.1.3.2 Myelosuppression

Idasanutlin was associated with myelosuppression (thrombocytopenia, neutropenia, anemia, and aplasia) in Study NP27872, evaluating idasanutlin in patients with solid tumors.

**Thrombocytopenia**

MDM2 antagonists were shown in vitro to affect all types of hematopoietic progenitors, including megakaryocytic differentiation. They inhibit both early and late stages of megakaryopoiesis, including ploidization and proplatelet formation (Mahfoudhi et al. 2016). As a consequence, the effect on early progenitors might induce long-lasting thrombocytopenia in vivo. Clinical data on the severity and duration of thrombocytopenia with idasanutlin are limited. Study NP27872, evaluating idasanutlin in patients with solid tumors, has shown possible exposure-dependent thrombocytopenia with an association between AUC/cycle and platelet nadir of the first cycle treatment for the daily dosing schedule, together with AUC/cycle as a determinant for Grade ≥4 thrombocytopenia. The potential relation between thrombocytopenia and hemorrhagic events has not been confirmed.

**Neutropenia and Febrile Neutropenia**

In Study NP27872, a possible exposure-dependent neutropenia was shown, with AUC/cycle as a determinant for Grade 4 neutropenia within the first two cycles in the daily schedule.

Blood counts will be monitored closely throughout study treatment (see the schedules of activities in Appendix 1 and Appendix 2); a Grade ≥3 decrease in neutrophil levels should be followed until resolution (to Grade ≥2 or baseline value) and additional measures considered as clinically indicated (see Section 5.1.8). Use of hematopoietic growth factors is encouraged during study treatment, particularly for patients who experience a first event of Grade ≥3 neutropenia during the study treatment phase. *Guidelines for treatment and primary prophylaxis with G-CSF are provided in Section 4.4.1.*

#### 5.1.3.3 Infections

Infections of various etiologies (including infections with fatal outcome) have been reported in patients treated with idasanutlin, primarily in patients with AML. The disease under study itself is associated with impaired immune function and increased susceptibility to infections. Assessment of causality for these cases can be difficult, and it is unclear whether or how much the incidence could be increased due to idasanutlin treatment. Because of the potential of idasanutlin to induce myelosuppression, patients should be carefully screened for evidence of active or uncontrolled infection or other uncontrolled disorder prior to enrollment. Patients in this study will be closely monitored for infection, and prompt therapy will be instituted as necessary. In any patient with uncontrolled and/or severe diarrhea, the presence of *C. difficile* infection should be investigated.

#### 5.1.3.4 Tumor Lysis Syndrome

There is a potential for TLS in patients treated with idasanutlin. Laboratory evidence of TLS has been reported for patients with AML treated in Study NP28679 and in patients considered to be at high risk of TLS owing to initial high WBC count. Clinical features were rare. For TLS-specific management and recommendations, refer to Section 5.1.6.

#### 5.1.3.5 Electrolyte Disorders

Electrolyte disorders (hypercalcaemia, hyperkalaemia, hypernatraemia, hypocalcaemia, hypokalaemia, hypomagnesaemia, hyponatremia, hyperphosphataemia, and hypophosphataemia) were commonly observed in patients treated with idasanutlin. In addition to institutional guidelines, electrolytes should be monitored during the treatment phase. Electrolyte disorders should be treated according to institutional guidelines.

#### 5.1.3.6 Other Adverse Events

Other adverse events commonly reported with idasanutlin included fatigue/asthenia, pyrexia, peripheral edema, headache, dyspnea, dizziness, and chills. These adverse events have been of mild severity and controllable with symptomatic treatment and/or nutritional support.

### 5.1.4 Risks Associated with Venetoclax

Phase I experience with venetoclax has demonstrated that it is generally well tolerated, and toxicities appear to be mostly manageable and/or reversible; see the Investigator's Brochure for more information. On the basis of clinical data to date, the following known and suspected risks with venetoclax are described. Guidelines for the management of these risks through dose and schedule modifications are described in Section 5.1.8.

#### 5.1.4.1 Tumor Lysis Syndrome

To date, the principal adverse reaction associated with venetoclax in the ongoing, single-agent Phase I dose-escalation study M12-175 has been TLS (primarily, but not exclusively, related to the first dose). TLS, including cases that have led to clinical sequelae and death, has been observed in patients with CLL at venetoclax doses of $\geq$50 mg.

Very few cases of nonclinically relevant electrolyte changes (e.g., elevated phosphate levels marginally above the ULN and 25% changes from baseline in uric acid levels that remained within the normal reference range) have been observed in NHL patients to date. However, TLS is a risk for patients with NHL who are treated with high cell-killing agents. Risk is highest for patients with bulky disease, elevated leukocyte count, elevated pretreatment LDH levels, compromised renal function, and dehydration. In this study, TLS will be monitored closely (see Section 5.1.6 and the schedules of activities in Appendix 1 and Appendix 2).

#### 5.1.4.2 Cytopenia

Effects on lymphocyte numbers are expected on the basis of the mechanism of action, and modest reductions in neutrophils have been observed with venetoclax therapy in patients. Thrombocytopenia and anemia have been reported with venetoclax in the ongoing Phase I, single-agent, dose-escalation study M12-175 that is being conducted in heavily pretreated patients with CLL and NHL. In most cases, the condition was preexisting. Adverse events of neutropenia and thrombocytopenia, including Grade $\geq 3$ events, have been reported in the oncology studies, with a slightly higher frequency in studies in which venetoclax was combined with other chemotherapeutic agents. In this study, blood counts will be monitored closely throughout treatment (see the schedules of activities in Appendix 1 and Appendix 2).

#### 5.1.4.3 Infectious Complications

Infections of various types have occurred in patients in the ongoing Phase I, single-agent dose-escalation study M12-175. NHL can be associated with impaired immune function and increased infections. Patients in this study will be closely monitored for infections, and prompt therapy will be instituted as necessary.

#### 5.1.4.4 Effects on Cardiac Function

Nonclinical studies demonstrated decreases of approximately 20% in cardiac function in healthy laboratory animals. No pattern of adverse events indicating changes in cardiac function has been reported in clinical studies to date. However, the number of patients exposed and the duration of exposure are still relatively low. Patients enrolled in this study are required to have ECGs and assessments of left ventricular ejection fraction at screening and as clinically indicated thereafter.

#### 5.1.4.5 Effects on Fertility

There is a potential for decreased spermatogenesis. Male patients who are considering preservation of fertility should bank sperm before treatment with venetoclax. Male patients must refrain from sperm donation starting from initial study drug administration until $3$ months after the last dose of $study\ treatments$. The long-term effects of venetoclax on either male or female reproductive potential are unknown.

### 5.1.5 Risk of Overlapping Toxicities

The overlapping toxicities from the combined administration of obinutuzumab or rituximab, idasanutlin, and venetoclax are anticipated during study treatment phase. Overlapping toxicities across obinutuzumab, idasanutlin, and venetoclax are myelosuppression (thrombocytopenia, neutropenia, and febrile neutropenia), infectious complications, TLS, and GI disorders (diarrhea, nausea, and vomiting; see Table 13). Overlapping toxicities across rituximab, idasanutlin, and venetoclax are myelosuppression (thrombocytopenia, neutropenia, and febrile neutropenia), TLS, and infections (Table 14). Such events should be closely monitored and managed throughout the study.

## Table 13 Overlapping Toxicities: Obinutuzumab, Idasanutlin, and Venetoclax

| | Idasanutlin [a] QD × 5 d "All Comers" Monotherapy in Solid Tumors (n = 38) | | Venetoclax [b] Monotherapy NHL (n = 128) | | Obinutuzumab [c] Monotherapy NHL (n = 215) | |
|---|---|---|---|---|---|---|
| Adverse Event | Overall % | Grade ≥ 3 Events | Overall % | Grade ≥ 3 Events | Overall % | Grade ≥ 3 Events |
| Thrombocytopenia | 47% | 45% | 14% | 10% | 18% | 5%-8% |
| Neutropenia/ febrile neutropenia | 24%/ 12% | 24%/ 12% | 20%/ 2.3% | 13%/ 2.3% | 36%/ 5% | 5%-14%/ 3% |
| Infections (SOC) | 27% | 9% | 40% | 11% | 43% | 3% |
| Diarrhea | 68% | 8% | 42% | 3% | 5%-8% | NA |
| Nausea/ vomiting | 68%/ 50% | 13%/ 3% | 46%/ 20% | NA | 5%-9%/ 5% | NA |
| TLS | NA [d] | NA [d] | 2% | 2% | 1% | 1% |

AML = acute myeloid leukemia; MTD = maximum tolerated dose; NA = not applicable; NHL = non-Hodgkin's lymphoma; QD × 5 d = once a day every 5 days; SOC = System Organ Class; TLS = tumor lysis syndrome.

[a] Study NP27872: All patients dosed for 5 days (includes dose-escalation and biomarker cohorts). This includes 20 patients treated above the MTD of 250 mg (Idasanutlin Investigator's Brochure, Version 7, July 2015).

[b] Study M12-175 (Arm B), M13-834, M13-835 (Investigator's Brochure, Version 7, 15 February 2016).

[c] Study BO21003 (final Clinical Study Report).

[d] Five TLS cases reported in Study NP28679 (Phase I study of idasanutlin in AML).

**Table 14 Overlapping Toxicities: Rituximab, Idasanutlin, and Venetoclax**

| | Idasanutlin [a] QD × 5 d "All Comers" Monotherapy in Solid Tumors (n = 38) | | Venetoclax [b] Monotherapy NHL (n = 128) | | Rituximab [c] Monotherapy (n = 356) | |
|---|---|---|---|---|---|---|
| Adverse Event | Overall % | Grade ≥ 3 Events | Overall % | Grade ≥ 3 Events | Overall % | Grade ≥ 3 Events |
| Thrombocytopenia | 47% | 45% | 14% | 10% | 9.6% | 1.7% |
| Neutropenia/ febrile neutropenia | 24%/ 12% | 24%/ 12% | 20%/ 2.3% | 13%/ 2.3% | 11.2%/ <1% | 4.2%/ <1% |
| Infections (SOC) | 27% | 9% | 40% | 11% | 30.3% | 3.9% |
| Nausea/ vomiting | 68%/ 50% | 13%/ 3% | 46%/ 20% | NA | 17.1%/ 6.3% | 0.3%/ 0.3% |
| TLS | NA [d] | NA [d] | 2% | 2% | <1% | <1% |

AML = acute myeloid leukemia; MTD = maximum tolerated dose; NA = not applicable; NHL = non-Hodgkin's lymphoma; QD × 5 d = once a day every 5 days; SOC = System Organ Class; TLS = tumor lysis syndrome.

[a] Study NP27872: All patients dosed for 5 days (includes dose-escalation and biomarker cohorts). This includes 20 patients treated above the MTD of 250 mg (Idasanutlin Investigator's Brochure, Version 7, July 2015).

[b] Study M12-175 (Arm B), M13-834, M13-835 (Investigator's Brochure, Version 7, 15 February 2016).

[c] Data from rituximab monotherapy in oncology trials.

[d] Five TLS cases reported in Study NP28679 (Phase I study of idasanutlin in AML).

#### 5.1.5.1 Thrombocytopenia

Theoretical synergistic effects on megakaryopoiesis are to be expected with combination therapy. Thrombocytopenia has been defined as an on-target PK/PD effect for idasanutlin, potentially inhibiting early progenitors. Venetoclax given as monotherapy spares Bcl-XL–induced thrombocytopenias. Emerging data from Study GO27878 with venetoclax in combination with CHOP and either rituximab or obinutuzumab suggest that the frequency and severity of thrombocytopenias are greater than previously expected. Thrombocytopenia is also an identified risk with obinutuzumab and rituximab, with the greatest risk being present during the first cycle of therapy. Fatal hemorrhages have been reported in patients being treated with obinutuzumab.

Therefore, owing to the potential severity and duration of thrombocytopenia induced by the study treatment combination, blood counts will be performed regularly (see the schedule of activities in Appendix 1 and Appendix 2). Anticoagulant and antiplatelet agents are not allowed during study treatment period. For patients who experience thrombocytopenia, close count monitoring should be performed until resolution. Other

measures (e.g., dose delays; see Section 5.1.8) or platelet transfusions should be considered as clinically indicated.

#### 5.1.5.2 Neutropenia and Febrile Neutropenia

There is a theoretical concern for synergistic neutropenia when venetoclax, idasanutlin, and obintuzumab or rituximab are used in combination therapy. Neutropenia has been reported in patients treated with idasanutlin with an apparent exposure response, with AUC/cycle as a determinant for Grade 4 neutropenia probability. Neutropenia is an identified risk with both venetoclax and obinutuzumab, and to a lesser extent with rituximab. Incoming data from Study GO27878, with venetoclax in combination with CHOP and either rituximab or obinutuzumab, indicate that venetoclax in combination with obinutuzumab and CHOP resulted in a higher than anticipated reporting of neutropenia and febrile neutropenia (in the setting of mandatory G-CSF prophylaxis), resulting in a modification of the venetoclax dosing regimen from QD dosing to a non-continuous 10-day dosing.

In anticipation of a potential increase in both the duration and intensity of neutropenia with the study treatment combination, adherence to the blood count schedule is required throughout study treatment (see the schedule of activities in Appendix 1 and Appendix 2). Severe events of Grade $\geq$3 neutropenia are to be carefully monitored and managed as clinically indicated (see Section 5.1.8). Use of G-CSF as primary prophylaxis for neutropenia (starting at Cycle 3 and continuing through each additional cycle of study treatment) in the dose-escalation phase, or as primary prophylaxis in each cycle of therapy for the expansion phase may be considered as clinically appropriate and is required for patients who experience a first event of Grade $\geq$3 neutropenia during the study treatment period (see Section 5.1.8).

#### 5.1.5.3 Infectious Complications

Patients with B-cell NHL and DLBCL have an intrinsic susceptibility for infections (including opportunistic infections). Serious infections, including cytomegalovirus (CMV), have been reported in patients treated with venetoclax in combination with rituximab or obinutuzumab. Infections were prevalent in patients who received treatment with idasanutlin, venetoclax, and/or obinutuzumab. No clear link has been established between serious infectious events and neutropenia. Patients should be carefully screened for evidence of active or uncontrolled infections prior to enrollment. Patients receiving antimicrobial agents with therapeutic intent are not permitted to begin study treatment (see Section 4.1.2).

If clinically indicated, anti-infective prophylaxis for viral, fungal, bacterial, or pneumocystis infections should be administered. Patients who experience infections of any degree on study treatment combination should be carefully observed and managed conservatively.

#### 5.1.5.4 Gastrointestinal Disorders

Diarrhea has been the most common adverse events reported across indications during idasanutlin clinical experience. It is very common, with acute onset, and is rarely severe. Diarrhea was also a common event reported during the venetoclax NHL combination studies. Clinical monitoring for potential diarrhea complications is required. Patients who develop diarrhea should have other or concomitant causes ruled out (including infection due to *C. difficile*), and if appropriate, prompt treatment with antidiarrheal agents must be administered (see Section 5.1.8).

Supportive therapies, including prophylaxis for diarrhea and nausea, are encouraged in this study. Electrolyte monitoring, correction, and IV hydration are advisable should GI events arise during treatment. Owing to the high incidence of diarrhea, *C. difficile* infections could go unnoticed. In the event of uncontrolled and/or severe diarrhea, it is advised to test for microbiological evidence of *C. difficile*. If presence is confirmed, aggressive therapy (e.g., metronidazole, vancomycin, fidaxomicin) should be introduced according to individual patient risk.

#### 5.1.5.5 Tumor Lysis Syndrome

There is the identified risk of TLS with obinutuzumab or venetoclax treatment since these agents can result in the rapid destruction of a large number of tumor cells. Idasanutlin has been linked to tumor lysis events in AML patients. Therefore, overlapping toxicity in regard to TLS cannot be excluded. Guidelines for management of patients who develop TLS are provided in Section 5.1.6. Risks of TLS with rituximab are very low (see Table 14).

### 5.1.6 Prophylaxis and Monitoring for Tumor Lysis Syndrome

TLS is a risk for patients with NHL who are treated with high cell-killing agents, including venetoclax. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Risk is highest for patients with bulky disease, elevated leukocyte count, elevated pretreatment LDH levels, compromised renal function, and dehydration. Assessment of tumor burden with CT scan and CBC with WBC differential, as well as blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine), should be performed in all patients and correct preexisting chemistry abnormalities prior to initiation of treatment with venetoclax.

All patients must receive prophylaxis for TLS before the initiation of the first dose of venetoclax (see also Section 4.3.2.5). Prophylaxis will include the following:

- Appropriate hydration, consisting of a fluid intake of approximately 2–3 L/day starting 24–48 hours before the start of treatment
- Administration of an agent to reduce uric acid (such as allopurinol 300 mg/day orally beginning 72 hours before dose and continuing for 3−7 days afterwards) or

rasburicase IV (for those high risk patients with elevated uric acid levels before treatment, or when otherwise judged to be appropriate by the investigator) until normalization of serum uric acid and other laboratory evidence of TLS (e.g., elevated serum LDH levels)

- Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities before the first dose of venetoclax, or the patient should receive additional prophylactic treatment and hydration before the initiation of dosing
- Patient at higher risk of TLS will be hospitalized for the initial venetoclax dose. Patients not considered at higher risk of TLS may be hospitalized after discussion with the investigator and Medical Monitor

On the day of the initial visit with administration of venetoclax (Day 1 of Cycle 1), serial vital signs, serum chemistry, and hematology samples will be drawn before the dose of venetoclax and 8 and 24 hours following the dose (see Appendix 1 and Appendix 2). These samples are to be sent immediately to the laboratory and the investigator or designee must review the results promptly. Laboratory values obtained prior to venetoclax dosing are to be used to determine whether a patient developed a change related to TLS. Laboratory results obtained 24 hours post-dose must be reviewed before receiving the dose of venetoclax on that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring according to the guidance in Appendix 12, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome.

In addition, if TLS is observed in the initial cohorts, staggering the dosing of venetoclax may be explored (venetoclax dosing may be initiated 2 or 3 days after the first idasanutlin dose during the first cycle of therapy), or starting at a lower dose of venetoclax and reaching the specified dose in a step-wise fashion after discussion with the Medical Monitor to prevent or promptly treat TLS.

### 5.1.7 Prophylaxis and Monitoring for All Patients

#### 5.1.7.1 Guidelines for Hospitalization of Patients at Risk for Tumor Lysis Syndrome

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

- Any lymph mass $\geq$ 10 cm in size on the screening CT scan
- Circulating lymphoma cells, defined by out of range (high) absolute lymphocyte count (ALC) or the presence of abnormal cells in the peripheral blood differential signifying circulating lymphoma cells

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

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

Hospitalization is not mandatory for patients exhibiting these characteristics, but these and any other factors considered relevant to TLS should be considered in the overall assessment of a patient's state and the risk of TLS. Investigators should use their judgment in assessing the risk of TLS for their patients and may optionally hospitalize any patient they consider to be at risk of TLS for the first dose of venetoclax, with approval of the Medical Monitor.

#### 5.1.7.2 Hospitalization Procedures

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

Serial vital signs will be measured and TLS laboratory samples will be drawn (serum chemistry as defined in Section 4.5.6) before the first dose administration of venetoclax and 8, 12, and 24 hour post-dose. In addition, hematology samples will be drawn 8 and 24 hours post-dose (see Appendix 1 and Appendix 2). Samples are to be sent immediately to the laboratory and the investigator or designee must review the results promptly. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results obtained 24 hours post-dose must be reviewed before administration of the dose of venetoclax on that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring according to the guidance in Appendix 12.

For patients assessed by the investigator to be at particularly high risk of TLS may, in addition to hospitalization, the investigator after discussion with the Medical Monitor may stagger the dosing of venetoclax (venetoclax dosing may be initiated 2 or 3 days after the first idasanutlin dose during the first cycle of therapy), or start the patient at a lower dose of venetoclax and reach the specified dose in a step-wise fashion.

### 5.1.8 Management of Patients Who Experience Specific Adverse Events

Patients should be assessed clinically before each study treatment administration.

Guidelines for management of toxicities are based on laboratory values obtained within 48 hours prior to Day 1 of each scheduled drug administration or within 24 hours prior to Days 8 and 15 of Cycle 1. Dosing will occur only if a patient's clinical assessment and laboratory test values are acceptable.

During induction, study treatment may be delayed for toxicity for a maximum of 21 days. If study treatment is delayed for more than 21 days, obinutuzumab or rituximab, idasanutlin, and venetoclax treatment will be permanently discontinued (see Table 18).

There will be no dose reductions of obinutuzumab or rituximab. Treatment delays apply to all toxicities described below; dose modifications apply only to toxicities that are considered to be related to either idasanutlin and/or venetoclax. The dose of idasanutlin may be reduced as outlined in Table 15. The dose of venetoclax may also be reduced.

In parallel cohorts, in which one drug only is escalated, the dose of that drug can be reduced only once per treatment cycle. In diagonal cohorts, in which the doses of both drugs have been escalated, the dose of both drugs will be reduced once per treatment cycle. There will be no more than one dose reduction per treatment cycle. If the doses of idasanutlin and venetoclax are reduced, re-escalation is not permitted.

**Table 15 Idasanutlin Dose-Reduction Steps**

| | Dose Reduction in Milligrams | | |
|---|---|---|---|
| Initial Dose | Step 1 | Step 2 | Step 3 |
| 100 mg | Minus 50 mg | No further reduction [a] | No further reduction [a] |
| 150 mg | Minus 50 mg | No further reduction [a] | No further reduction [a] |
| 200 mg | Minus 50 mg | Minus 50 mg | No further reduction [a] |
| 250 mg | Minus 100 mg | Minus 50 mg | No further reduction [a] |
| 300 mg | Minus 100 mg | Minus 50 mg | Minus 50 mg |
| 350 mg | Minus 100 mg | Minus 100 mg | Minus 50 mg |
| 400 mg | Minus 100 mg | Minus 100 mg | Minus 50 mg |

[a] When no further idasanutlin dose reduction is possible, the patient will be discontinued from the study.

The dose of venetoclax will be reduced by at least 25% from the current dose (rounded to the lower closest 50 mg) or return to the previous dose, with a minimum final dose of 200 mg. If the dose level reaches 200 mg, no further reduction will be allowed and the patient will be discontinued from the study.

Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications. Guidelines for management of toxicities during induction treatment are provided in Section 5.1.8.1 and during consolidation or maintenance treatment in Section 5.1.8.2.

### 5.1.8.1 Toxicities during Induction Treatment

#### Hematologic Toxicities during Induction Treatment

Guidelines for management of hematologic toxicities that occur during induction treatment, with the exception on Days 8 and 15 of Cycle 1 when obinutuzumab are given in Table 16. Hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia. Lymphopenia is not considered a hematologic toxicity but an expected outcome of therapy.

## Table 16 Guidelines for Management of Hematologic Toxicities That Occur during Induction Treatment (Except on Days 8 and 15 of Cycle 1)

| Event | Action to Be Taken |
|---|---|
| Grade 3 or 4 hematologic toxicity [a, b] | **For patients who have had one or no prior dose reductions:**<br>• Withhold study treatment. [a]<br>• Administer RBCs or platelets as required.<br>• If patient has not already initiated G-CSF, initiate prophylactic G-CSF for current and subsequent cycles.<br>• If improvement to Grade ≤2 or baseline within ≤14 days after the scheduled date for the next cycle, resume obinutuzumab or rituximab at full dose and resume idasanutlin and venetoclax at current dose.<br>• If improvement to Grade ≤2 or baseline 15–21 days after the scheduled date for the next cycle, resume obinutuzumab or rituximab at the full dose and resume the last escalated drug(s) at a reduced dose according to guidelines in Section 5.1.8.1 for current and subsequent cycles.<br>No more than three dose reductions of idasanutlin or venetoclax are allowed.<br>• If study treatment is withheld for >21 days, permanently discontinue study treatment.<br>• Permanently discontinue study treatment if any of the following events occur:<br>– Grade 3 or 4 thrombocytopenia of any duration if associated with Grade ≥ 3 bleeding<br>– Recurrent Grade 3 or 4 neutropenia if associated with fever of >38°C for >5 days) or a documented infection despite use of G-CSF and after one idasanutlin dose reduction and/or one venetoclax dose reduction or reduced schedule<br>– Recurrent Grade 4 neutropenia or thrombocytopenia lasting more than 7 days despite use of G-CSF (for neutropenia) and after one idasanutlin dose reduction and/or one venetoclax dose reduction/reduced schedule<br>**For patients who present with recurrent Grade 3 thrombocytopenia/neutropenia in consecutive cycles:**<br>If despite the use of G-CSF, for subsequent cycles, modify the venetoclax dose by reducing to next dose level or decrease the dosing schedule; reduce idasanutlin to the next dose level (see guidelines in Section 5.1.8.1).<br>**For patients who have had reductions in three doses (either as single drug dose reduction or double drug reduction in the same time) or for patients who reach the lowest dose level and no further dose reduction is applicable (see Section 5.1.8):**<br>• Permanently discontinue study treatment. |

G-CSF = granulocyte colony-stimulating factor.

[a] Treatment delays apply to all toxicities; dose modifications apply only to toxicities that are considered to be related to any of the study treatment components.

[b] If cytopenia is thought to be caused mainly by B-cell lymphoma infiltration of the bone marrow, the investigator may decide not to reduce idasanutlin or venetoclax doses.

## Table 17 Guidelines for Management of Hematologic Toxicities That Occur on Days 8 and 15 of Cycle 1

| Event | Action to Be Taken |
|---|---|
| Febrile neutropenia or neutropenia with infection | • Withhold obinutuzumab and venetoclax until resolution of fever and infection (as applicable) and resume at the next scheduled dose.<br>• *If the patient has not already initiated G-CSF, initiate prophylactic G-CSF for current and subsequent cycles.* [b]<br>• If the dose on Day 8 of Cycle 1 is delayed by ≤2 days, Day 15 of Cycle 1 should be delayed by the same number of days to retain the treatment interval for obinutuzumab.<br>• If the dose on Day 8 of Cycle 1 is delayed by >2 days, omit the Day 8 dose and administer the Day 15 dose as previously scheduled (if infection or neutropenic fever have resolved).<br>• If the dose on Day 15 of Cycle 1 is delayed by >2 days, omit the Day 15 dose and administer the next dose (Day 1 of Cycle 2) of obinutuzumab, venetoclax, and idasanutlin as scheduled (if infection or neutropenic fever has resolved).<br>• If the event is ongoing on Day 1 of Cycle 2, follow the instructions in Table 18.<br>Note: Obinutuzumab and venetoclax should not be withheld for asymptomatic neutropenia. |
| Severe thrombocytopenia [a] or symptomatic bleeding (irrespective of platelet count) | • Withhold obinutuzumab and venetoclax until platelet count is ≥50,000 cells/μL with resolution of bleeding and resume at the next scheduled dose.<br>• Consider prophylactic or therapeutic platelet transfusion as appropriate<br>• In patients with HLA sensitization, HLA-compatible platelet transfusions should be administered.<br>• If the dose on Day 8 of Cycle 1 is delayed by ≤2 days, Day 15 of Cycle 1 should be delayed by the same number of days to retain the treatment interval for obinutuzumab.<br>• If the dose on Day 8 of Cycle 1 dose is delayed by >2 days, omit the Day 8 dose and administer the Day 15 dose as previously scheduled (if severe thrombocytopenia and/or symptomatic bleeding have resolved).<br>• If the dose on Day 15 of Cycle 1 is delayed by >2 days, omit the Day 15 dose and administer the next dose (Day 1 of Cycle 2) of obinutuzumab, venetoclax, and idasanutlin as scheduled (if severe thrombocytopenia and/or symptomatic bleeding have resolved).<br>• If the event is ongoing at Day 1 of Cycle 2, follow instructions in Table 18. |

*G-CSF = granulocyte colony-stimulating factor;* HLA = human leukocyte antigen; QD = once a day.

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

[b] *In the dose-escalation phase, prophylactic G-CSF should start after Cycle 2.*

### Non-Hematologic Toxicities during Induction Treatment

Guidelines for management of non-hematologic toxicities that occur during induction treatment are presented in Table 18.

## Table 18 Guidelines for Management of Non-Hematologic Toxicities

| Event | Action to Be Taken |
|---|---|
| General guidance for treatment delays, discontinuation, and resumption | • If study treatment is withheld for >21 days because of a toxicity that is attributable to study treatment, permanently discontinue study treatment.<br>• Permanently discontinue study treatment for Grade 4 events.<br>• When a treatment cycle is delayed because of toxicity resulting from any component of the regimen, all study treatment should be held and resumed together to remain synchronized.<br>• Dosing may be resumed after resolution to Grade ≤1 or baseline status. Resumption of dosing without complete resolution of toxicity may be considered in special circumstances after having obtained Medical Monitor agreement. |
| IRRs and anaphylaxis | • Guidelines for the management of IRRs are provided in Section 5.1.1.1. In case of Grade 4 IRRs or anaphylaxis, study treatment should be permanently discontinued. |
| Clinical and laboratory TLS | Grade 4 events:<br>• Permanently discontinue study treatment in the case of Grade 4 events.<br>Grade ≤ 3 events:<br>• Withhold study treatment. [a]<br>• Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.<br>• If symptoms (laboratory and clinical) have resolved completely, resume obinutuzumab or rituximab at full dose and resume venetoclax and idasanutlin at current dose. |
| New-onset neurologic manifestations suggestive of PML | • Withhold study treatment. [a]<br>• Consult with a neurologist if PML is suspected (refer to Section 5.1.1.5 for guidance on investigations).<br>• If PML is ruled out, resume obinutuzumab or rituximab at the full dose and resume idasanutlin and venetoclax at the current dose.<br>• If PML is confirmed, permanently discontinue study treatment. |

**Table 18 Guidelines for Management of Non-Hematologic Toxicities (cont.)**

| | |
|---|---|
| AST, ALT, or bilirubin increase: | Grade 4 events:<br>• Permanently discontinue study treatment in the case of Grade 4 events.<br>Grade 2 or 3 events (or $\geq 10 \times$ ULN for patients with liver involvement):<br>• Withhold study treatment. [a]<br>• If improvement to Grade $\leq 1$ (or $\leq 5 \times$ ULN (Grade 2) for patients with liver involvement), resume obinutuzumab or rituximab and idasanutlin at full dose and resume venetoclax at next lower dose [a] for current and subsequent cycles per guidelines in Section 5.1.8. No more than three dose reductions of venetoclax are allowed. Patients who have had three prior dose reductions of venetoclax and/or idasanutlin should be permanently discontinued. Permanently discontinue study treatment for life-threatening liver toxicity (including Hy'sLaw cases). |
| Diarrhea | Grade 4 diarrhea: permanently discontinue study treatment. |

IRR = infusion-related reaction; PML = progressive multifocal leukoencephalopathy; ULN = upper limit normal.

[a] Treatment delays apply to all events; dose modifications apply only to events that are considered to be related to any of the study treatment components.

[b] Clinical judgment should prevail, reserved for events having a significant effect on a patient's clinical situation, and upon consultation with the Medical Monitor.

**Table 18 Guidelines for Management of Non-Hematologic Toxicities (cont.)**

| Event | Action to Be Taken |
|---|---|
| Diarrhea (cont.) | Grade 2 or 3 diarrhea:<br>• If Grade 3 diarrhea occurs between Days 1 and 5 of the treatment cycle, withhold study treatment only if diarrhea does not improve to Grade ≤2 within 48 hours with appropriate treatment. After the study treatment is withheld, if diarrhea improves to Grade ≤2, resume obinutuzumab or rituximab at the full dose and resume idasanutlin and venetoclax at a reduced dose according to guidelines in Sections 5.1.8.1 and 5.1.8.2 for current and subsequent cycles.<br>• If Grade 3 diarrhea is present at the time of the next planned cycle, withhold study treatment. If diarrhea improves to Grade ≤2, resume obinutuzumab or rituximab at full dose and resume idasanutlin and venetoclax at a reduced dose according to guidelines in Sections 5.1.8.1 and 5.1.8.2 for current and subsequent cycles.<br>Management for diarrhea:<br>• Rule out other or concomitant causes, including, but not limited to, medications, *Clostridium difficile* infection, malabsorption/lactose intolerance, fecal impaction, and dietary supplements high in fiber.<br>• Initiate treatment at the time of onset.<br>• Administer loperamide 4 mg as loading dose; and up to 2 mg every 4 hours or after every unformed stool (for a maximum daily dose of 16 mg), or per institutional standard.<br>• For subsequent episodes, use 4 mg QD prophylactic loperamide 30 minutes before subsequent dosing. If diarrhea persists after 48 hours despite administration of the maximum recommended daily loperamide dose (16 mg/24 hr), second-line agents may be considered (diphenoxylate, atropine, octreotide, budesonide, or tincture of opium).<br>Encourage patients to hydrate abundantly and self-medicate with loperamide 2 mg in the event that diarrhea recurs (up to 2 mg every 4 hours or after every unformed stool for a maximum daily dose of 16 mg), or per institutional standard.<br>• Monitor electrolyte levels closely and correct as appropriate.<br>• Administer IV fluids as clinically indicated.<br>• Upon presentation of Grade 3 diarrhea or diarrhea persists for >24 hours despite maximum recommended daily loperamide dose, exclude presence of active infections (e.g., *C difficile*). If present, treat infection(s), according to local guidelines. |

IRR = infusion-related reaction; PML = progressive multifocal leukoencephalopathy; ULN = upper limit normal.

[a] Treatment delays apply to all events; dose modifications apply only to events that are considered to be related to any of the study treatment components.

[b] Clinical judgment should prevail, reserved for events having a significant effect on a patient's clinical situation, and upon consultation with the Medical Monitor.

**Table 18 Guidelines for Management of Non-Hematologic Toxicities (cont.)**

| Event | | Action to Be Taken |
|---|---|---|
| Nausea and vomiting | | Grade 4 vomiting:<br>• Permanently discontinue study treatment.<br>Grade 1, 2, or 3 vomiting or nausea:<br>• Consider prophylaxis with second-generation anti-emetics like palonosetron, ondansetron, or granisetron.<br>• If vomiting occurs within 15 minutes of taking idasanutlin and/or 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 (see Sections 5.1.8.1 and 5.1.8.2). |
| Dermatologic toxicity | | Permanently discontinue rituximab in the event of Stevens-Johnson syndrome or toxic epidermal necrolysis. |
| Other non-hematologic toxicities (i.e., not described above), excluding alopecia | Grade 3 or 4 | Grade 4 events<br>• Permanently discontinue study treatment.<br>Grade 3 events<br>• Withhold study treatment. [a]<br>If improvement to Grade ≤1 or baseline, resume obinutuzumab or rituximab at the full dose and resume idasanutlin and venetoclax at reduced (Section 5.1.8) dose [a] for subsequent cycles. No more than three dose reductions of idasanutlin or venetoclax are allowed.<br>**For patients who have had three prior dose reductions (either as a single drug dose reduction or double drug reduction in the same time) or for patients who reach the lowest dose level and no further dose reduction is applicable (See Section 5.1.8):**<br>• Permanently discontinue study treatment. |
| | Grade 2 | • Withhold study treatment. [a, b]<br>• If improvement to Grade ≤1 or baseline, resume obinutuzumab or rituximab at the full dose and resume idasanutlin and venetoclax at the current dose. |

IRR = infusion-related reaction; PML = progressive multifocal leukoencephalopathy; ULN = upper limit normal.

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

[b] Clinical judgment should prevail, reserved for events having a significant effect on a patient's clinical situation, and upon consultation with the Medical Monitor.

#### 5.1.8.2 Toxicities during Maintenance or Consolidation Treatment

Guidelines for management of toxicities that occur during maintenance or consolidation treatment are presented in Table 19.

**Table 19 Guidelines for Management of Toxicities That Occur during Maintenance or Consolidation Treatment**

| Event | Action to Be Taken |
|---|---|
| Hematologic toxicity: Grade 3 or 4 | • Withhold study treatment.<br>• Administer myeloid growth factors for neutropenia as allowed according to institutional guidelines.<br>• Administer RBCs or platelets as required.<br>• If improvement to Grade ≤2, resume obinutuzumab or rituximab at full dose and resume venetoclax at next lower dose for subsequent cycles per guideline in Section 5.1.8. Patients who are not eligible for further venetoclax dose reductions should be permanently discontinued.<br>• If study treatment is withheld for >42 days, permanently discontinue study treatment.<br>• Withdraw venetoclax and idasanutlin in case of recurrent episodes of Grade ≥3 thrombocytopenia and/or neutropenia. |
| Non-hematologic toxicity: Grade ≥2 | • Withhold study treatment.<br>• If improvement to Grade ≤1 or baseline, resume obinutuzumab or rituximab at full dose and resume venetoclax at the next lower dose for subsequent cycles per guideline in Section 5.1.8. Patients who are not eligible for further venetoclax and/or idasanutlin dose reductions should be permanently discontinued.<br>• If study treatment is withheld for >42 days, permanently discontinue study treatment. |

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

### 5.2.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

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

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

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

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

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

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

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

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of any of the study treatment components is suspected.
- TLS of any grade, irrespective of causality
- Grade $\geq$3 neutropenia, including febrile neutropenia
- Grade $\geq$3 thrombocytopenia or Grade $\geq$2 thrombocytopenia if associated with hemorrhage or bleeding)
- Grade 2 diarrhea
- Grade $\geq$2 *C. difficile* infection
- Second malignancies

### 5.2.4 Selected Adverse Events

Selected adverse events in this study are defined as adverse events for which additional data collection or analyses will be performed. Selected adverse events do not require immediate reporting if they are not serious or meet the adverse events of special interest definition (see Section 5.2.3).

The following adverse events are considered selected adverse events:

- Thrombocytopenia, including acute thrombocytopenia (events occurring during and within 24 hours following an obinutuzumab infusion)

- Hepatitis B reactivation
- Cardiac events
- TLS
- IRRs
- All infections, including PML
- Neutropenia, including prolonged neutropenia (neutropenia $<$1000 cells/$\mu$L that does not resolve after 28 days without obinutuzumab treatment) and late-onset neutropenia (neutropenia $<$1000 cells/$\mu$L occurring $\geq$28 days after obinutuzumab treatment has been completed or stopped)
- GI perforation

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

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

### 5.3.1 Adverse Event Reporting Period

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

**After informed consent** has been obtained **but prior to initiation of study treatment**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

**After initiation of study treatment**, all adverse events will be reported until 90 days after the last dose of study treatment, and Grade 3 or 4 infections (related and unrelated) in patients who received obinutuzumab will continue to be reported until up to 2 years after the last dose of obinutuzumab.

Second malignancies will be recorded indefinitely for patients who received obinutuzumab (even if the study has been closed) (see Section 5.6).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

### 5.3.2 Eliciting Adverse Event Information

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

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

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

### 5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 20 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 20 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE**

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

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

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

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

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

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

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

### 5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an

adverse event is considered to be related to any of the study treatment components, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

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

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

### 5.3.5 Procedures for Recording Adverse Events

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

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

#### 5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after the end of study treatment infusion and are judged to be related to infusion of any of the study treatment components should be captured as a diagnosis (e.g., “infusion-related reaction”) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction.” Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

#### 5.3.5.2 Diagnosis versus Signs and Symptoms

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

report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

#### 5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

#### 5.3.5.4 Persistent or Recurrent Adverse Events

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

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

#### 5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

#### 5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

#### 5.3.5.7 Abnormal Liver Function Tests

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

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

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

#### 5.3.5.8 Deaths

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

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should

be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

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

#### 5.3.5.9 Preexisting Medical Conditions

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

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

#### 5.3.5.10 Lack of Efficacy or Worsening of Lymphoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should **not** be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the modified Lugano 2014 criteria (see Appendix 4). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

#### 5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or insertion of access device for study treatment administration)

  This includes planned hospitalization for TLS prophylaxis and monitoring (i.e., on Day 1 of Cycle 1 hospitalization)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

#### 5.3.5.12 Adverse Events Associated with an Overdose or Error in Treatment Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event *(see Section 5.4.4)*. Additionally, all adverse events associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

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

Limited experience with doses higher than the approved IV doses of rituximab is available from clinical trials in humans. The highest IV dose tested in humans is 5000 mg (2250 mg/$m^2$). No additional safety signals were identified.

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

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to any of the study treatments:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- DLTs (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)
- *Overdoses, medication errors, drug abuse, or drug misuse (see Section 5.4.4 for details on reporting requirements)*

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

### 5.4.1 Emergency Medical Contacts

**Medical Monitor Contact Information for All Sites**

Medical Monitor/Roche Medical Responsible: [redacted], M.D., Ph.D. (Primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

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

### 5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

#### 5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided

to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

#### 5.4.2.2 Events That Occur after Study Treatment Initiation

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

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

Instructions for reporting serious adverse events that occur $>$90 days after the last dose of study treatment are provided in Section 5.6.

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 18 months after the last dose of study treatment for those *treated with* obinutuzumab, idasanutlin, and venetoclax and within 12 months after the last dose of study treatment for those *treated with* rituximab, idasanutlin, and venetoclax. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### 5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of study treatment. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

#### 5.4.3.3 Abortions

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

#### 5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

### 5.4.4 *Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse*

*Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:*

- *Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose*
- *Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose*
- *Medication error: accidental deviation in the administration of a drug*

  *In some cases, a medication error may be intercepted prior to administration of the drug.*

- *Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm*
- *Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse*

  *In cases where drug is to be self administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.*

*Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For idasanutlin, obinutuzumab or rituximab, and venetoclax, adverse events associated with special situations should be recorded as described below for each situation:*

- *Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.*
- *Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.*
- *Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.*
- *Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.*
- *Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.*
- *Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.*
- *Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.*

*In addition, all special situations associated with idasanutlin, obinutuzumab or rituximab, and venetoclax, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:*

- *Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.*

- *Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.*
- *Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.*
- *Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.*
- *Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.*
- *Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.*
- *Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.*
- *Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.*
- *Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.*
- *Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.*

*As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.*

## 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

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

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

### 5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## 5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 90 days after the last dose of study drug), all deaths, regardless of cause, should be reported on the Long-Term Survival Follow-Up eCRF. Grade 3 and 4 infections (related and unrelated) in patients who received obinutuzumab should be reported on the Adverse Event eCRF until up to 2 years after the last dose of obinutuzumab. In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior study treatment, the event should be reported through use of the Adverse Event eCRF. The sponsor should also be notified of events of second malignancies indefinitely (even if the study has been closed) for patients who received obinutuzumab.

The investigator should report any other events (excluding related serious adverse events 90 days after the last dose of study treatment if the investigator becomes aware of any event and Grade 3 and 4 infections, independently of causality, for 2 years) directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

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

- Obinutuzumab Investigator's Brochure
- Rituximab IV Oncology Investigator's Brochure
- Idasanutlin Investigator's Brochure
- Venetoclax Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Study data will be summarized separately for dose escalation and expansion phase. Data from the dose-escalation phase will be summarized by dose level and regimen. Data from the expansion phase will be summarized by histologic subtype (i.e., FL or DLBCL).

## 6.1 DETERMINATION OF SAMPLE SIZE

### 6.1.1 Dose Escalation

Dose finding will be conducted during the dose-escalation phase of this study. The estimated sample size follows from the dose-escalation rules for a mCRM with over dose control (Thall et al. 2003; Neuenschwander et al. 2015). It is anticipated that enrollment of up to eight cohorts of 3–6 patients each, for a total of 9–60 patients, will be required to meet the Part 1 study objective. This number is an approximation based upon assumptions and experience from other similar dose-finding studies. More details on the dose-escalation design and its operating characteristics are given in Section 3.1.2.3 and Appendix 6. The estimated probability to require more than 50 patients in the investigated scenarios in the protocol is generally $<5\%$.

### 6.1.2 Expansion Cohorts

Approximately 80 patients (40 patients with FL and 40 patients with DLBCL) will be enrolled during the expansion phase.

The primary efficacy analysis for the expansion phase will be estimation of the true proportion of patients expected to obtain a PET-defined CR at EOI. A sample size of 40 patients is deemed sufficient to provide adequate precision for the point estimate and for the lower end of the 90% CI to rule out a clinically uninteresting probability of response of $<40\%$ in FL, and 40% in DLBCL assuming an observed PET-defined CR rate of 55%. Table 21 provides 90% Clopper-Pearson exact CIs for the probability of

achieving a PET-defined CR at the EOI for a range of observed proportions based on a sample of 40 patients.

**Table 21 Potential 90% CI for the True Probability of Achieving a PET-CT−Defined Complete Response at End of Induction for n = 40**

| Observed Proportion of Patients Achieving a PET-CT−Defined CR at EOI | Two-Sided 90% Clopper-Pearson CI [a] for True Population PET-CT−Defined CR |
|---|---|
| 0.32 | (0.20, 0.46) |
| 0.50 | (0.36, 0.64) |
| 0.55 | (0.40. 0.68) |
| 0.60 | (0.46, 0.73) |
| 0.65 | (0.51, 0.77) |
| 0.70 | (0.56, 0.82) |
| 0.72 | (0.58, 0.83) |
| 0.75 | (0.61, 0.86) |
| 0.80 | (0.66, 0.89) |
| 0.85 | (0.72, 0.93) |

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

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

## 6.2 SUMMARIES OF CONDUCT OF STUDY

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

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

## 6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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

## 6.4 SAFETY ANALYSES

The primary safety objectives are to determine the RP2D dose of idasanutlin and venetoclax in combination with obinutuzumab or rituximab during the dose-escalation

phase and to evaluate the safety and tolerability of the triplet combination across all phases of the study.

The safety analysis population will include all patients who have received at least one dose of any component of the combination, whether patients are prematurely withdrawn from the study or not. All safety parameters will be summarized and presented in tables based on this safety population.

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

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

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

## 6.5 EFFICACY ANALYSES

The primary and secondary efficacy analyses will be performed and will include all patients enrolled in the expansion phase who receive one dose of any component of the combination. Data from patients who were dosed at the RP2D and selected regimen during the dose-escalation phase may be pooled with the corresponding arm of the expansion phase, depending on their indication.

Response will be determined on the basis of PET-CT scans or CT scans alone, using the modified Lugano 2014 criteria (see Appendix 4).

### 6.5.1 Primary Efficacy Endpoint

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

### 6.5.2 Secondary Efficacy Endpoints

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

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

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

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

### 6.5.3 Exploratory Efficacy Endpoints

Exploratory efficacy analyses will include an estimation of the proportion of patients achieving the following endpoint:

- For patients who have positive PET scans at EOI:

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

  CR at EOC, as determined by the IRC and by the investigator on the basis of PET-CT scans, in patients with DLBCL

Additional descriptive analysis based on TP53 mutation status will be performed on the following endpoint:

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

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

Exploratory efficacy analyses will also be performed on the following endpoints (see definitions in Section 2.2.3):

- PFS
- EFS
- DFS
- OS

PFS, EFS, DFS, and OS will be summarized descriptively using the Kaplan-Meier method (Kaplan and Meier 1958). For the PFS, EFS, and DFS analyses, data for patients without an event of interest will be censored at the date of the last tumor assessment. For patients without post-baseline tumor assessments, data will be censored at the date of initiation of study treatment plus 1. For the OS analysis, data for

patients who have not died will be censored at the date the patient was last known to be alive. When medians are reached, the corresponding estimated median will be provided, along with the 95% CI using the method of Brookmeyer and Crowley (1982). In addition, estimates of the proportion of patients who are event free at 6 months, 9 months, 1 year, and 2 years will be provided, along with 95% asymptotic CIs using Greenwood's formula for standard errors.

## 6.6 PHARMACOKINETIC ANALYSES

The PK analyses will include patients with sufficient data to enable estimation of key parameters (e.g., AUC, time to maximum concentration [$t_{max}$], $C_{max}$, and half-life), with patients grouped according to treatment received.

Serum concentrations of obinutuzumab or rituximab, or plasma concentrations of idasanutlin or venetoclax will be tabulated, summarized, and plotted after appropriate grouping. As appropriate, PK parameters (e.g., AUC, $t_{max}$, $C_{max}$, and half-life) may also be calculated, tabulated, and summarized after appropriate grouping. Additional PK and PK/PD analyses (e.g., population modeling that includes pooled analyses across studies) may also be performed as appropriate. If performed, these additional analyses may be reported separately from the CSR. At the discretion of the Sponsor, all analyses may be extended to include relevant biotransformation products of idasanutlin and/or venetoclax.

## 6.7 BIOMARKER ANALYSES

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

## 6.8 INTERIM ANALYSES

During the expansion phase, predictive probabilities may be used to guide early stopping for futility by comparing the observed proportion of patients who achieve a PET-CT–defined CR at EOI with that in historical controls. The design is based on Lee and Liu (2008), with the modification that the uncertainty in historical control data is fully taken into account by utilizing a distribution on the control response rate. Interim analysis decision rules will be based on the predictive probability that this trial will a positive outcome if carried out to completion and will use the historical control data available at the time of analysis.

It is anticipated that least one interim analysis per disease indication will be conducted during the expansion phase of the study, with the earliest interim analysis taking place when at least 15 patients treated have been evaluated for a PET-CT–defined CR at EOI. If, at any interim analysis, a low predictive probability suggests that the proportion of patients achieving a PET-CT–defined CR at EOI is lower than desired, the IMC will review the data and decide whether to recommend an early decision to stop enrollment.

Additional review of safety and/or efficacy data by the IMC may be requested by and carried out at the discretion of the Medical Monitor. Further details regarding the rules and guidelines of data will be provided in an IMC charter.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

## 7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

## 7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

## 7.4 USE OF COMPUTERIZED SYSTEMS

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

## 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by

relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

# 8. ETHICAL CONSIDERATIONS

## 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

## 8.2 INFORMED CONSENT

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

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

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

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

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

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

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

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

## 8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

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

## 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit).

# 9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

## 9.1 STUDY DOCUMENTATION

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

## 9.2 PROTOCOL DEVIATIONS

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

## 9.3 SITE INSPECTIONS

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

## 9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Roche.

An EDC system will be used for this study. An IxRS will be used to assign patient numbers. A central laboratory will be used for a subset of laboratory assessments as specified in Section 4.5.6; otherwise, local laboratories will be used. A central IRF will be used to collect PET-CT and CT scans, and the IRC will perform independent assessments of response for all patients enrolled in the study (a separate IRC charter will contain all details). Data from this study will be shared with an expert scientific committee that will provide scientific input for the benefit–risk assessment.

## 9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:

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

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective CSR. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country,

the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

## 9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

## 10. REFERENCES


Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16:2780–95.

Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol 2010;28:3360–5.

Beers SA, French RR, Chan HT, et al. Antigenic modulation limits the efficacy of anti-CD20 antibodies: implications for antibody selection. Blood 2010;115: 5191–201.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29–41.

Calabrese LH, Molloy ES, Huang D, et al. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum 2007;56:2116–28.

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

Carson KR, Bennett CL. Rituximab and progressive multi-focal leukoencephalopathy: the jury is deliberating. Leuk Lymphoma 2009;50:323–4. doi: 10.1080/10428190902779257.

Cheson B, Fisher R, Barrington S, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059–69.

Coiffier B, Thieblemont C, Van Der Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040–5.

Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. Nat Rev Cancer 2002;2:647–56.

Cory S, Huang DCS, Adams JM. The Bcl-2 family: roles in cell survival and oncogenesis. Oncogene 2003;22:8590–607.

Dalle S, Reslan L, Besseyre de Horts T, et al. Preclinical studies on the mechanism of action and the anti-lymphoma activity of the novel anti-CD20 antibody GA101. Mol Cancer Ther 2011;10:178–85.

Davis RE, Brown KD, Siebenlist U, et al. Constitutive nuclear factor kappB activity is required for survival of activated B cell-like diffuse large B cell lymphoma cells. J Exp Med 2001;194:1861–74.

Ding Q, Zhang Z, Liu JJ, et al. Discovery of RG7388, a potent and selective p53-MDM2 inhibitor in clinical development. J Med Chem 2013;56:5979–83.

Dreyling M, Ghielmini M, Marcus R. Newly diagnosed and relapsed follicular lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2014;25:iii76–82.

Dunleavy K, Fanale M, LaCasce A, et al. Preliminary report of a multicenter prospective Phase II study of DA-EPOCH-R in MYC-rearranged aggressive B-cell lymphoma [abstract]. 56th ASH Annual Meeting 2014; Abstract 395.

Dyer M, Grigg A, Gonzales M, et al. Obinutuzumab (GA101) in combination with cyclophosphamide, doxorubicine, vincristine and prednisone (CHOP) or bendamustine in patients with previously untreated follicular lymphoma (FL): results of the Phase Ib GAUDI study (BO21000) [abstract]. 54th ASH Annual Meeting 2012; Abstract 3686.

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

Fenaux P, Preudhomme C, Quiquandon I, et al. Mutations of the *P53* gene in acute myeloid leukaemia. Br J Haematol 1992;80:178–83.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49:1374–403.

Gascoyne RD, Adomat SA, Krajewski S, et al. Prognostic significance of Bcl-2 protein expression and Bcl-2 gene rearrangement in diffuse aggressive non-Hodgkin's lymphoma. Blood 1997;90:244–51.

Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184–90.

Goldberg SL, Pecora AL, Alter RS, et al. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 2002;99:1486–8.

Green TM, Young KH, Visco C. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3450–7.

Haldar S, Basu A, Croce CM. Serine-70 is one of the critical sites for drug-induced Bcl2 phosphorylation in cancer cells. Cancer Res 1998;58:1609–15.

Harris SL, Levine AJ. The p53 pathway: positive and negative feedback loops. Oncogene 2005;24:2899–908.

Herter S, Birk M, Klein C, et al. Glycoengineering of therapeutic antibodies enhances monocyte/macrophage-mediated phagocytosis and cytotoxicity. J Immunol 2014;192:2252–60.

Herting F, Friess T, Bader S, et al. Enhanced anti-tumor activity of the glycoengineered Type II CD20 antibody obinutuzumab (GA101) in combination with chemotherapy in xenograft models of human lymphoma. Leuk Lymphoma 2014;55:2151–60.

Herting F, Herter S, Friess T, et al. Antitumour activity of the glycoengineered type II anti-CD20 antibody obinutuzumab (GA101) in combination with the MDM2-selective antagonist idasanutlin (RG7388). Eur J Haematol 2016; 97:461–70.

Hu G, Zhang W, Deisseroth AB. P53 gene mutations in acute myelogenous leukaemia. Br J Haematol 1992;81:489–94.

Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from the International DLBCL Rituximab-CHOP Consortium Program. Blood 2013;121:4021–31.

Ichikawa A, Kinoshita T, Watanabe T, et al. Mutations of the p53 gene as a prognostic factor in aggressive B-cell lymphoma. N Engl J Med 1997;337:529–34.

Imamura J, Miyoshi I, Koeffler P. p53 in hematologic malignancies. Blood 1994;84: 2412–21.

Iqbal J, Meyer PN, Smith L, et al. BCL2 predicts survival in germinal center B-cell-like diffuse large B-cell lymphoma treated with CHOP-like therapy and rituximab. Clin Cancer Res 2011;17:7785–95.

Iqbal J, Neppali VT, Wright G, et al. *BCL2* expression is a prognostic marker for the activated B-cell–like type of diffuse large B-cell lymphoma. J Clin Oncol 2006;24:961–8.

Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012:30:3452–9.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

Kojima K, Konopleva M, Samudio IJ, et al. MDM2 antagonists induce p53-dependent apoptosis in AML: implications for leukemia therapy. Blood 2005;106:3150–9.

Kostakoglu L, Goy A, Martinelli G, et al. Post-induction therapy FDG-PET is prognostic for progression-free survival in relapsed follicular lymphoma: a preliminary analysis of Gauss study. EHA 2014, Abstract S561.

Ladetto M, Bruggemann M, Monitillo L, et al. Next-generation sequencing and real-time quantitative PCR for minimal residual disease detection in B-cell disorders. Leukemia. 2014;6:1299–307.

Lee JJ, Liu DD. A predictive probability design for Phase II cancer clinical trials. Clin Trials 2008;5:93–106.

Lenz G, Wright G, Dave SS, et al. Stromal gene signature in large B-cell lymphomas. N Engl J Med 2008;359:2313–23.

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630–6.

Mahfoudhi E, Lordier L, Marty C, et al. P53 activation inhibits all types of hematopoietic progenitors and all stages of megakaryopoiesis. Oncotarget 3 March 2016, doi: 10.18632/oncotarget.7881 [Epub ahead of print].

Martinelli G, Pappayannidis C, Yee K, et al. Phase 1b results of idasanutlin + cytarabine in acute myeloid leukemia patients. Presented at the European Hematology Association 21st Congress, 11 June 2016.

Møller MB, Gerdes AM, Skjødt K, et al. Disrupted p53 function as predictor of treatment failure and poor prognosis in B- and T-cell non-Hodgkin's lymphoma. Clin Cancer Res 1999;5:1085–91.

Mössner E, Brünker B, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new Type II anti-CD20 antibody with enhanced direct and immune effector cell–mediated B-cell cytotoxicity. Blood 2010;115:4393–402.

Neuenschwander B, Matano A, Tang Z, et al. A Bayesian industry approach to Phase I combination trials in oncology. In: Statistical methods in drug combination studies. Wei Zhao W, Yang Y, editors. Boca Raton (FL): Chapman & Hall/CRC Biostatistics Series 2015; Chapter 6:120.

Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2013;31:2103–9.

Oren M. Decision making by p53: life, death and cancer. Cell Death Differ 2003;10:431–42.

Patz M, Isaeva P, Forcob N, et al. Comparison of the in vitro effects of the anti-CD20 antibodies rituximab and GA101 on chronic lymphocytic leukaemia cells. Br J Haematol 2011;152:295–306.

Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol 2011;12:1013–22.

Poruchynsky MS, Wang EE, Rudin CM, et al. Bcl-xL is phosphorylated in malignant cells following microtubule disruption. Cancer Res 1998;58:3331–8.

Ray-Coquard I, Blay JY, Italiano A, et al. Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study. Lancet Oncol 2012; 13:1133–40.

Reed JC. Bcl-2 family proteins and hematologic malignancies: history and future malignancies: history and future prospects. Blood 2008;111:332 –30.

Reis B, Jukofsky L, Chen G, et al. Acute myeloid leukemia patient response to idasanutlin (RG7388) is associated with pre-treatment MDM2 protein expression in leukemic blasts. Haematologica 2016;101:e185–8.

Roschewski M, Stetler-Stevenson M, Yuan C, et al. Minimal residual disease: what are the minimum requirements? J Clin Oncol 2014;32:475–6.

Salles G, Seymour J, Feugier P, et al. Updated 6 year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immunochemotherapy. Blood 2013;122: Abstract 509.

Sampath D, Herter S, Hertig F, et al. Combination of the glycoengineer Type II CD20 antibody obintuzumab (GA101) and the novel Bcl-2 selective inhibitor GDC-0199 results in superior in vitro and in vito anti-tumor activity in models of B-cell malignancies [poster]. Presented at the annual meeting of the American Society of Hematology, Poster 4412, 9 December 2013, New Orleans.

Savage KJ, Johnson NA, Ben-Neriah S, et al. *MYC* gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood 2009;114:3533–7.

Schuetz JM, Johnson NA, Morin RD, et al. BCL2 mutations in diffuse large B-cell lymphoma. Leukemia 2012;26:1383–90.

Sehn L. A second anti-CD20 drug for NHL. Cancer Discov. 2015 Jun 2. [Epub ahead of print].

Siegel R, Naishadham D, Jemal A. Cancer statistics 2013. CA Cancer J Clin 2013;63:11–30.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205.

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

Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013; 19:202–8.

Thall PF, Millikan RE, Mueller P, et al. Dose-finding with two agents in Phase I oncology trials. Biometrics 2003;59:487–96.

Thomas A, Gingrich RD, Smith BJ, et al. 18-Fluoro-deoxyglucose positron emission tomography report interpretation as predictor of outcome in diffuse large B-cell lymphoma including analysis of 'indeterminate' reports. Leuk Lymphoma 2010;51:439–46.

Tovar C, Rosinski J, Filipovic Z, et al. Small molecule MDM2 antagonists reveal aberrant p53 signaling in cancer: implications for therapy. Proc Natl Acad Sci USA 2006;3:1888–93.

Trněný M, Bouabdallah K, Dueck G et al. Obinutuzumab plus bendamustine versus bendamustine alone in patients with rituximab-refractory follicular lymphoma: Results from Gadolin study. 21st EHA Annual Meeting. Abstract S440.

Trotman J, Luminari S, Boussetta S. Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies. Lancet Haematol 2014;1:17–27.

Valente LJ, Aubrey BJ, Herold MJ, et al. Therapeutic response to non-genotoxic activation of p53 by Nutlin3a is driven by PUMA-mediated apoptosis in lymphoma cells. Cell Rep 2016;14:1858–66.

Vassilev LT. MDM2 inhibitors for cancer therapy. Trends Mol Med 2007;13:23–31.

Vassilev LT, Vu BT, Graves B, et al. In vivo activation of the p53 pathway by small molecule antagonists of MDM2. Science 2004;303:844–8.

Visco C, Tzankov A, Xu-Monette ZY, et al. Patients with diffuse large B-cell lymphoma of germinal center origin with BCL2 translocations have poor outcome, irrespective of MYC status: a report from an International DLBCL Rituximab-CHOP Consortium Program Study. Haematologica 2013;98:255–63.

Vitolo U, Chiappella A, Bellò M, et al. The outcome of patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab-CHOP (R-CHOP) is not predicted by 18-FDG-positron emission tomography/computerized tomography (PET) performed at intermediate in-course evaluation, but only by PET assessed at the end of therapy. Blood (ASH Annual Meeting Abstracts) 2010;116:Abstract 2819.

Wattel E, Preudhomme C, Hacquet B, et al. P53 mutations are associated with resistance to chemotherapy and short survival in hematologic malignancies. Blood 1994;84:3148–57.

Wertz IE, Kusam S, Lam C, et al. Sensitivity to antitubulin chemotherapeutics is regulated by MCL1 and FBW7. Nature 2011;471:110–4.

Xu-Monette ZY, Wu L, Visco C, et al. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with R-CHOP: report from an International DLBCL Rituximab-CHOP Consortium Program Study. Blood 2012;120: 3986–96.

Yang H, Filipovic Z, Brown D, et al. Macrophage inhibitory cytokine-1: a novel biomarker for p53 pathway activation. Mol Cancer Ther 2003;2:1023–9.

Young KH, Leroy K, Moller MB, et al. Structural profiles of TP53 gene mutations predict clinical outcome in diffuse large B-cell lymphoma: an international collaborative study. Blood 2008:112:3088–98.

Zelenetz AD, Abramson JS, Advani RH, et al. NCCN clinical practice guidelines in oncology: non-Hodgkin lymphoma, v1. 2014. NCCN clinical practice guidelines in oncology: non-Hodgkin's lymphomas. J Natl Compr Canc Netw 2010;8:288–334.

Zelenetz AD, Salles G, Mason KD, et al. Phase Ib study of venetoclax plus R- or G-CHOP in patients with B-cell non-Hodgkin lymphoma [poster]. Proc Am Soc Clin Oncol 2016:poster 7566.

Zhong J, Chen G, Jukofsky L, et al. MDM2 antagonist clinical response association with a gene signature in acute myeloid leukaemia. Br J Haematol 2015;171:432–5.

Zhou Z, Sehn LH, Rademaker A, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood 2014;123:837–42.

# Appendix 1
# Schedule of Activities for Patients with Follicular Lymphoma: Dose-Escalation and Expansion Phases

| Assessment/Procedure | Screening [a] | | Induction (Six 28-Day Cycles) | | | | | | | | EOI | | EOM [b] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 (±1 day) | | | | Cycle 2 (±2 days) | | Cycles 3–6 (±2 days) | | | | | | |
| | Days −28 to −1 | Days −14 to −1 | D 1 | D 5 | D 8 | D 15 | D 1 | D 15 | D 1 | D 15 | After Last Induction Dose [c] | Maintenance (24 Months) [d] | 35 Days after Last Dose | Post-Tx Follow-Up Period (Q3M) [e] | Survival Follow-Up Period (Q3M) [e] |
| Informed consent(s) [f] | x | | | | | | | | | | | | | | |
| Demographic data | x | | | | | | | | | | | | | | |
| Medical history | x | | | | | | | | | | | | | | |
| ECOG performance status | x | | | | | | | | | | | | | | |
| Vital signs [g] | x | | x | | x | x | x | | x | | x [h] | x [i] | x | | |
| Height | x | | | | | | | | | | | | | | |
| Weight and BSA | x | | | | | | | | | | | | | | |
| Triplicate12-Lead ECG | x | | x [j] | x [j] | | | | | x [j] | | x | x [j] | x | | |
| MUGA or ECHO | x [k] | | | | | | | | x [k] | | x [k] | | x [k] | | |
| Complete physical examination [l, m] | x | | | | | | | | | | | | | | |
| Targeted physical examination [m, n] | | | | | | | Day 1, Cycles 2 and 4 | | | | x | x [i] | x | x | |
| Ann Arbor, FLIPI, and FLIPI2 | x | | | | | | | | | | | | | | |
| B symptoms [o] | x | | | | | | | | | | | | | | |

# Appendix 1
# Schedule of Activities for Patients with Follicular Lymphoma: Dose-Escalation and Expansion Phases (cont.)

| Assessment/Procedure | Screening [a] | | Induction (Six 28-Day Cycles) | | | | | | | | EOI | Maintenance (24 Months)[d] | EOM [b] | Post-Tx Follow-Up Period (Q3M) [e] | Survival Follow-Up Period (Q3M) [e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 (±1 day) | | | | Cycle 2 (±2 days) | | Cycles 3–6 (±2 days) | | | | | | |
| | Days −28 to −1 | Days −14 to −1 | D 1 | D 5 | D 8 | D 15 | D 1 | D 15 | D 1 | D 15 | After Last Induction Dose [c] | | 35 Days after Last Dose | | |
| $\beta_2$ microglobulin | | | x | | | | | | | | | | | | |
| Hematology [p] | | x | x [q,r] | | x [r] | x [r] | x [r] | x | x [r] | x | x [h] | x [i] | x | | |
| Serum chemistry [s] | | x | x [q,r] | | x [r] | x [r] | x [r] | x | x [r] | x | x [h] | x [i] | x | | |
| Coagulation (INR, aPTT [or PTT], and PT) | | x | | | | | | | | | | | | | |
| Pregnancy test [t] | | x | | | | | | | | | x [h] | | x | | |
| Hepatitis B and C, testing [u] | x | | | | | | | | | | | | | | |
| Quantitative IgA, IgG, and IgM | | | x | | | | | | | | x | x [v] | x | x [w] | |
| PK sample for obinutuzumab | | | x [x] | | | | | | | | | | | | |
| PK sample for idasanutlin | | | x [x] | | | | | | | | | | | | |
| PK sample for venetoclax | | | x [x] | | | | | | | | | | | | |
| Exploratory biomarker samples | | | x [x] | | | | | | | | | | | | |

# Appendix 1
# Schedule of Activities for Patients with Follicular Lymphoma: Dose-Escalation and Expansion Phases (cont.)

| Assessment/Procedure | Screening [a] | | Induction (6 Cycles; 28-Day Cycles) | | | | | | | | EOI | | EOM [b] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 (±1 day) | | | | Cycle 2 (±2 days) | | Cycles 3–6 (±2 days) | | | | | | |
| | Days −28 to −1 | Days −14 to −1 | D 1 | D 5 | D 8 | D 15 | D 1 | D 15 | D 1 | D 15 | After Last Induction Dose [c] | Maintenance (24 Months) [d] | 35 Days after Last Dose | Post-Tx Follow-Up Period (Q3M) [e] | Survival Follow-Up Period (Q3M) [e] |
| Blood for MRD [y] | | | x [r] | | | | x | | | | x | x [v] | x | | |
| Blood for lymphocyte immunophenotyping [z] | | | x [r] | | | x [r] | x [r] | | x [r] | | x | x [v] | x | x [w] | |
| Optional serum for RBR [aa] | | | x | x | | | | | | | | | | | |
| Tumor tissue specimen (remaining tissue may be used for optional RBR specimen [bb]) | x [bb] | | x [cc] | | | | | | | | | | | | |
| Concomitant medications | x | | To be recorded continually until end of treatment | | | | | | | | | | | | |
| Adverse events [dd] | x | | To be assessed continualy [dd] | | | | | | | | | | | | |
| PET-CT scan | x [ee] | | | | | | | | | | x [ff] | x [gg] | | | |
| CT scan [hh] | x [hh] | | | | | | x [ii] | | | | x [ff] | x [jj] | x [kk] | x [ll] | |
| Bone marrow biopsy and aspirate | x [mm] | | | | | | | | | | x [ff, nn] | x [nn] | x [kk, nn] | | |
| New anti-lymphoma treatment | | | | | | | | | | | | | | x | x |
| Survival follow-up | | | | | | | | | | | | | | | x |

# Appendix 1
# Schedule of Activities for Patients with Follicular Lymphoma: Dose-Escalation and Expansion Phases (cont.)

BSA = body surface area; CT = computed tomography; D = day; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOI = end of induction; EOM = end of maintenance; FL = follicular lymphoma; FLIPI (2) = Follicular Lymphoma International Prognostic Index (2); MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PET = positron emission tomography; PK = pharmacokinetic; Q3M = every 3 months; RBR = Roche Biosample Repository; TLS = tumor lysis syndrome; Tx = treatment.

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

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

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

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

[d] Maintenance treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity for up to 2 years.

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

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

[g] Vital signs include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. For obinutuzumab infusions: For the first cycle and for patients who experience an infusion-related reaction, vital signs will be measured prior to the infusion, every 15 (±5) minutes for the first 90 minutes of the infusion, and then every 30 (±10) minutes until 1 hour after completion of the infusion. For the second and subsequent cycles, vital signs will be measured every 30 minutes during the infusion, except for patients who have experienced an infusion-related reaction during a prior infusion. For venetoclax, serial vital signs will be measured and TLS laboratory samples will be drawn (serum chemistry as defined in Section 4.5.6) prior to the first dose of venetoclax and 8, 12, and 24 hour post-dose.

[h] Perform only for patients who will not be receiving maintenance treatment.

# Appendix 1
# Schedule of Activities for Patients with Follicular Lymphoma: Dose-Escalation and Expansion Phases (cont.)

[i] Vital signs will be measured, a targeted physical examination will be performed, and hematology and serum chemistry will be assessed during maintenance every 2 weeks during the first month, every month until Month 6, and every 2 months thereafter.

[j] All ECGs should be performed within 2 hours prior to idasanutlin administration and either 6 hours after idasanutlin administration or immediately after obinutuzumab administration, whichever occurs later. ECGs will be performed in triplicate on Days 1 and 5 of Cycles 1 and 4 in the induction phase. However, on Day 5 of Cycles 1 and 4 in the induction phase, the postdose ECG should be performed only if the patient is still at the clinic.

[k] Perform MUGA or echocardiogram at screening (Day −28 to Day −1), on Day 1, Cycle 4, at the EOI, the EOM, and as clinically indicated.

[l] Includes evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

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

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

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

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

[q] Screening laboratory assessments may be used for Day 1 of Cycle 1 if performed within 24 hours prior to Day 1 of Cycle 1. Additional hematology and serum chemistry samples must be drawn 0–4 hours pre-dose and 8 and 24 hours post-dose on Day 1 of Cycle 1 to monitor for TLS. Note that the 24-hour post-dose sample will be obtained on Day 2 of Cycle 1.

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

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

[t] All women who are not post-menopausal ($\geq 12$ months of non–therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days prior to Day 1 of Cycle 1. Because of the suspected effect of idasanutlin or venetoclax on embryo–fetal development, monthly pregnancy testing is strongly recommended for women of childbearing potential.

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

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

[w] Perform every 3 months until recovery to either normal range or baseline level, disease progression, or the start of new anti-lymphoma treatment, whichever occurs first.

# Appendix 1
# Schedule of Activities for Patients with Follicular Lymphoma: Dose-Escalation and Expansion Phases (cont.)

[x] Refer to Appendix 3 for detailed schedule.
[y] Includes circulating lymphoma cells and/or cell-free circulating-tumor DNA.
[z] Includes B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and natural killer cell counts (CD16 and CD56).
[aa] Requires separate patient consent for RBR participation. Not applicable for a site that has not been granted approval for RBR sampling.
[bb] Availability of adequate archival or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.6 for details).
[cc] A tumor biopsy sample is preferred and recommended at the time of progression unless no adequate tumor site is accessible.
[dd] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment (see Section 5.6). An exception is made for Grade 3 and 4 infections (related and unrelated) in patients who received obinutuzumab, which should be reported until up to 2 years after the last dose of study treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to any of the study treatment components or trial-related procedures until a final outcome can be reported.
[ee] The screening PET-CT scan must be performed within 35 days prior to Day 1 of Cycle 1.
[ff] Perform only for patients who receive at least two cycles of induction treatment.
[gg] If PET-CT scan is positive at the EOI, perform 12 months after initiation of induction treatment, within 14 days prior to study treatment administration.
[hh] CT scan of the neck (if clinically indicated), chest, abdomen and pelvis. If contrast is medically contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans of the chest, abdomen, and pelvis (and neck, if clinically indicated) and a non-contrast CT scan of the chest may be performed. Combined PET/CT scanners may be used to collect diagnostic CT scans but only according to the technical guidelines in the imaging manual. Screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.
[ii] Perform within 7 days prior to Day 1 of Cycle 3.
[jj] Perform 12, 18, and 24 months after initiation of induction treatment, within 14 days prior to treatment administration.
[kk] Perform only if not done within the previous 3 months.
[ll] Perform every 6 months.
[mm] Bone marrow biopsy and aspirate must be performed within approximately 3 months prior to Day 1 of Cycle 1.
[nn] For patients with bone marrow involvement at screening, a repeat assessment will be performed at the EOI, during maintenance, or at the EOM whenever there is radiologic evidence of a complete response or if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression). Additional bone marrow assessments may be performed at the discretion of the investigator.

# Appendix 1
# Schedule of Activities for Patients with Follicular Lymphoma: Dose-Escalation and Expansion Phases (cont.)

## Study Treatment Administration: Dose Escalation before the Bridging Cohorts (Regimen A)

| | Induction (Six 28-Day Cycles) | | | | | | | | Maintenance Every 2 Months [a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cycle 1 (±1 day) | | | | | Cycles 2–6 (±2 days) | | | | | |
| Study Treatment | Day 1 | Day 5 | Day 8 | Day 10 | Day 15 | Day 1 | Day 5 | Day 10 | Day 1 | Day 5 | Day 10 |
| Obinutuzumab [b] (1000 mg IV) | x | | x | | x | x | | | x | | |
| Idasanutlin [b] (PO QD) | Days 1–5 | | | | | Days 1–5 | | | TBD [c] | | |
| Venetoclax [b] (PO QD) | Days 1–5 or Days 1–10 [d] | | | | | Days 1–5 or Days 1–10 [d] | | | TBD [c] | | |

IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PO = by mouth; QD = once a day; TBD = to be determined.

[a] Total duration of maintenance is 24 months for obinutuzumab and 6 months for idasanutlin and venetoclax.

[b] Refer to Section 4.3.2 for instructions on study treatment administration.

[c] Regimen will be defined based on available safety, tolerability, PK, and PD data.

[d] Regimen is defined according to the dose-escalation plan (see Section 3.1.2).

# Appendix 1
# Schedule of Activities for Patients with Follicular Lymphoma: Dose-Escalation and Expansion Phases (cont.)

## Study Treatment Administration: Dose Escalation for the Bridging Cohorts (Regimen B)

| | Induction (Six 28-Day Cycles) | | | | | | | | Maintenance Every 2 Months [a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cycle 1 (±1 day) | | | | | Cycles 2–6 (±2 days) | | | | | |
| Study Treatment | Day 1 | Day 5 | Day 8 | Day 10 | Day 15 | Day 1 | Day 5 | Day 10 | Day 1 | Day 5 | Day 10 |
| Obinutuzumab [b] (1000 mg IV) | x | | x | | x | x | | | x | | |
| Idasanutlin [b] (PO QD) | | | | | | Days 1–5 | | | TBD [c] | | |
| Venetoclax [b] (PO QD) | | | | | | Days 1–5 or Days 1–10 [d] | | | TBD [c] | | |

IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PO = by mouth; QD = once a day; TBD = to be determined.

[a] Total duration of maintenance is 24 months for obinutuzumab and 6 months for idasanutlin and venetoclax.

[b] Refer to Section 4.3.2 for instructions on study treatment administration.

[c] Regimen will be defined based on available safety, tolerability, PK, and PD data.

[d] Regimen is defined according to the dose-escalation plan (see Section 3.1.2).

# Appendix 1
# Schedule of Activities for Patients with Follicular Lymphoma: Dose-Escalation and Expansion Phases (cont.)

## Study Treatment Administration: Expansion Phase (Regimen A or Regimen B as defined after the escalation phase)

| | Induction (Six 28-Day Cycles) | | | | | | | | Maintenance Every 2 Months [a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cycle 1 (±1 day) | | | | | Cycles 2–6 (±2 days) | | | | | |
| Study Treatment | Day 1 | Day 5 | Day 8 | Day 10 | Day 15 | Day 1 | Day 5 | Day 10 | Day 1 | Day 5 | Day 10 |
| Obinutuzumab [b] (1000 mg IV) | x | | x | | x | x | | | x | | |
| Idasanutlin [b, c] (PO QD) | Days 1–5 | | | | | Days 1–5 | | | TBD [d] | | |
| Venetoclax [b, c] (PO QD) | Days 1–5 or Days 1–10 [e] | | | | | Days 1–5 or Days 1–10 [e] | | | TBD [d] | | |

IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PO = by mouth; QD = once a day; TBD = to be determined.

[a] Total duration of maintenance is 24 months for obinutuzumab and 6 months for idasanutlin and venetoclax.

[b] Refer to Section 4.3.2 for instructions on study treatment administration.

[c] May only be given in Cycles 2–6 if this regimen is chosen.

[d] Regimen will be defined based on available safety, tolerability, PK, and PD data.

[e] Regimen is defined according to the dose-escalation plan (see Section 3.1.2).

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phases

| Assessment/Procedure | Screening [a] | | Induction (Six 28-Day Cycles) | | | | | | | | EOI | Consol-idation (6 Mo) [d] | EOC [b] | Post-Tx Follow-Up Period (Q3M) [e] | Survival Follow-Up Period (Q3M) [e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 (±1 day) | | | | Cycle 2 (±2 days) | | Cycles 3–6 (±2 days) | | | | | | |
| | Days −28 to −1 | Days −14 to −1 | D 1 | D 5 | D 8 | D 15 | D 1 | D 15 | D 1 | D 15 | After Last Induction Dose [c] | | 35 Days after Last Dose | | |
| Informed consent(s) [f] | x | | | | | | | | | | | | | | |
| Demographic data | x | | | | | | | | | | | | | | |
| Medical history | x | | | | | | | | | | | | | | |
| ECOG performance status | x | | | | | | | | | | | | | | |
| Vital signs [g] | x | | x | | x | x | x | | x | | x [h] | x [i] | x | | |
| Height | x | | | | | | | | | | | | | | |
| Weight and body surface area | x | | | | | | | | | | | | | | |
| Triplicate 12-Lead ECG | x | | x [j] | x [j] | | | | | x [j] | | x | x [j] | x | | |
| MUGA or ECHO | x [k] | | | | | | | | x [k] | | x [k] | | x [k] | | |
| Complete physical examination [l, m] | x | | | | | | | | | | | | | | |
| Targeted physical examination [m, n] | | | | | | | Day 1, Cycles 2 and 4 | | | | x | x [i] | x | x | |
| Ann Arbor, IPI | x | | | | | | | | | | | | | | |
| B symptoms [o] | x | | | | | | | | | | | | | | |

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phases (cont.)

| Assessment/Procedure | Screening [a] | | Induction (Six 28-Day Cycles) | | | | | | | | EOI | Consol-idation (6 Mo) [d] | EOC [b] | Post-Tx Follow-Up Period (Q3M) [e] | Survival Follow-Up Period (Q3M) [e] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 (±1 day) | | | | Cycle 2 (±2 days) | | Cycles 3–6 (±2 days) | | | | | | |
| | Days −28 to −1 | Days −14 to −1 | D 1 | D 5 | D 8 | D 15 | D 1 | D 15 | D 1 | D 15 | After Last Induction Dose [c] | | 35 Days after Last Dose | | |
| $\beta_2$ microglobulin | | | x | | | | | | | | | | | | |
| Hematology [p] | | x | x [q, r] | | x [r] | x [r] | x [r] | x | x [r] | x | x [h] | x [i] | x | | |
| Serum chemistry [s] | | x | x [q, r] | | x [r] | x [r,t] | x [r] | x [t] | x [r] | x [t] | x [h] | x [i] | x | | |
| Coagulation (INR, aPTT [or PTT], and PT) | | x | | | | | | | | | | | | | |
| Pregnancy test [u] | | x | | | | | | | | | x [h] | | x | | |
| Hepatitis B and C, testing [v] | x | | | | | | | | | | | | | | |
| Quantitative IgA, IgG, and IgM | | | x | | | | | | | | x | x [w] | x | x [x] | |
| PK sample for obinutuzumab | | | x [y] | | | | | | | | | | | | |
| PK sample for rituximab | | | | | | | | | | | | | | | |
| PK sample for idasanutlin | | | x [y] | | | | | | | | | | | | |
| PK sample for venetoclax | | | x [y] | | | | | | | | | | | | |
| Exploratory biomarker sample | | | x [y] | | | | | | | | | | | | |
| Blood for MRD [z] | | | x [r] | | | | x | | | | x | x [w] | x | | |

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phases (cont.)

| Assessment/Procedure | Screening [a] | | Induction (Six 28-Day Cycles) | | | | | | | | EOI | | EOC [b] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cycle 1 (±1 day) | | | | Cycle 2 (±2 days) | | Cycles 3–6 (±2 days) | | | | | | |
| | Days −28 to −1 | Days −14 to −1 | D 1 | D 5 | D 8 | D 15 | D 1 | D 15 | D 1 | D 15 | After Last Induction Dose [c] | Consol-idation (6 Mo) [d] | 35 Days after Last Dose | Post-Tx Follow-Up Period (Q3M) [e] | Survial Follow-Up Period (Q3M) [e] |
| Blood for lymphocyte immunophenotyping [aa] | | | x [r] | | | x [r] | x [r] | | x [r] | | x | x [w] | x | x [x] | |
| Optional serum for RBR [bb] | | | x | x | | | | | | | | | | | |
| Tumor tissue specimen (remaining tissue may be used for optional RBR specimen) [cc] | x [cc] | | x [dd] | | | | | | | | | | | | |
| Concomitant medications | | | To be recorded continually until end of treatment | | | | | | | | | | | | |
| Adverse events [ee] | | | To be assessed continually [ee] | | | | | | | | | | | | |
| PET-CT scan | x [ff] | | | | | | | | | | x [gg] | | x [oo] | | |
| CT scan [hh] | x [hh] | | | | | | x [ii] | | | | x [gg] | x [jj] | x [kk] | x [ll] | |
| Bone marrow biopsy and aspirate | x [mm] | | | | | | | | | | x [gg, nn] | x [nn] | x [kk, nn] | | |
| New anti-lymphoma treatment | | | | | | | | | | | | | | x | x |
| Survival follow-up | | | | | | | | | | | | | | | x |

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phases (cont.)

BSA = body surface area; CT = computed tomography; D = day; DLBCL = diffuse large B-cell lymphoma; ECG = electrocardiogram; ECHO = echocardiogram; eCRF = electronic Case Report Form; ECOG = Eastern Cooperative Oncology Group; EOI = end of induction; EOC = end of consolidation; IPI = International Prognostic Index; MRD = minimal residual disease; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PET = positron emission tomography; PK = pharmacokinetic; Q3M = every 3 months; RBR = Roche Biosample Repository; TLS = tumor lysis syndrome; Tx = treatment.

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

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

[b] Patients who complete consolidation treatment or discontinue consolidation treatment prematurely will undergo assessments at the EOC.

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

[d] Consolidation treatment should start 8 weeks (±1 week) after Day 1 of the final cycle of induction and will continue until disease progression or unacceptable toxicity for up to 6 months.

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

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

[g] Vital signs include respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. For obinutuzumab infusions: For the first cycle and for patients who experience an infusion-related reaction, vital signs will be measured prior to the infusion, every 15 (±5) minutes for the first 90 minutes of the infusion, and then every 30 (±10) minutes until 1 hour after completion of the infusion. For the second and subsequent cycles, vital signs will be measured every 30 minutes during the infusion, except for patients who had experienced an infusion-related reaction during a prior infusion. For rituximab infusions: Vital sign monitoring during infusion should be determined as per local label.

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phases (cont.)

[h] Perform only for patients who will not be receiving consolidation treatment.
[i] Vital signs will be measured, a targeted physical examination will be performed, and hematology and serum chemistry will be assessed during consolidation every 2 weeks during the first month, every month until EOC.
[j] All ECGs should be performed within 2 hours prior to idasanutlin administration and either 6 hours after idasanutlin administration or immediately after obinutuzumab/rituximab administration, whichever occurs later. ECGs will be performed in triplicate on Days 1 and 5 of Cycles 1 and 4 in the induction phase. However, on Day 5 of Cycles 1 and 4 in the induction phase, the postdose ECG should be performed only if the patient is still at the clinic.
[k] Perform MUGA or echocardiogram at screening (Day −28 to Day −1), on Day 4, Cycle 4, at the EOI, the EOC, and as clinically indicated.
[l] Includes evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.
[m] As part of tumor assessment, the physical examination should include evaluation for the presence of enlarged nodes, palpable hepatomegaly, and splenomegaly. This information will be recorded on the appropriate Tumor Assessment eCRF.
[n] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
[o] Unexplained fever $>38°C$, night sweats, and unexplained weight loss $>10\%$ of body weight over 6 months.
[p] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent or absolute WBC differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).
[q] Screening laboratory assessments may be used for Day 1 of Cycle 1 if performed within 24 hours prior to Day 1 of Cycle 1. Additional hematology and chemistry samples must be drawn 0–4 hours pre-dose and 8 and 24 hours post-dose on Day 1 of Cycle 1 to monitor for TLS. Note that the 24-hour post-dose sample will be obtained on Day 2 of Cycle 1.
[r] Perform hematology and chemistry tests within 72 hours prior to Day 1 of each cycle and within 24 hours prior to Days 8 and 15 of Cycle 1. Samples for exploratory biomarker research should be collected at the same time as hematology and serum chemistry samples.
[s] Includes sodium, potassium, glucose, BUN or urea, creatinine, calculated creatinine clearance, calcium, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, amylase, lipase, LDH, and uric acid.
[t] Perform only for patients treated with obinutuzumab.
[u] All women who are not postmenopausal ($\geq 12$ months of non–therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days prior to Day 1 of Cycle 1. Because of the suspected effect of idasanutlin or venetoclax on embryo–fetal development, monthly pregnancy testing is strongly recommended for women of childbearing potential.
[v] Includes hepatitis B surface antigen, total hepatitis B core antibody, and hepatitis C virus antibody.
[w] Perform at the same time as tumor assessments at 3 months after initiation of consolidation treatment.

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phases (cont.)

[x] Perform every 3 months until recovery to either normal range or baseline level, disease progression, or the start of new anti-lymphoma treatment, whichever occurs first.
[y] Refer to Appendix 3 for detailed schedule.
[z] Includes circulating lymphoma cells and/or cell-free circulating-tumor DNA.
[aa] Includes B-cell counts (CD19), T-cell counts (CD3, CD4, and CD8), and natural killer cell counts (CD16 and CD56).
[bb] Requires separate patient consent for RBR participation. Not applicable for a site that has not been granted approval for RBR sampling.
[cc] Availability of adequate archival or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.6 for details).
[dd] A tumor biopsy sample is preferred and recommended at the time of progression unless no adequate tumor site is accessible.
[ee] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 90 days after the last dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment (see Section 5.6). An exception is made for Grade 3 and 4 infections (related and unrelated) in patients who received obinutuzumab, which should be reported until up to 2 years after the last dose of obinutuzumab. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to any of the study treatment components or trial-related procedures until a final outcome can be reported.
[ff] The screening PET-CT scan must be performed within 35 days prior to Day 1 of Cycle 1.
[gg] Perform only for patients who have received at least two cycles of induction treatment.
[hh] CT scan of the neck (if clinically indicated), chest, abdomen, and pelvis. If contrast is medically contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans of the chest, abdomen, and pelvis (and neck, if clinically indicated) and a non-contrast CT scan of the chest may be performed. Combined PET/CT scanners may be used to collect diagnostic CT scans but only according to the technical guidelines in the imaging manual. Screening CT scan must be performed within 35 days prior to Day 1 of Cycle 1.
[ii] Perform within 7 days prior to Day 1, Cycle 3.
[jj] Perform 3 months after initiation of consolidation treatment.
[kk] Perform only if not done within the previous 3 months.
[ll] Perform every 6 months.
[mm] Bone marrow biopsy and aspirate must be performed within approximately 3 months prior to Day 1 of Cycle 1.

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phases (cont.)

[nn] For patients with bone marrow involvement at screening, a repeat assessment will be performed at the EOI, during consolidation, or at the EOC whenever there is radiologic evidence of a complete response or if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression). Additional bone marrow assessments may be performed at the discretion of the investigator.

[oo] *A PET-CT scan should be performed at end of consoliation if the PET-CT scan is posiive at end of induction.*

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phase (cont.)

## Study Treatment Administration: Dose Escalation before the Bridging Cohorts

| Study Treatment | Induction (Six 28-Day Cycles) | | | | | | | | Consolidation Every 2 Months [a] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cycle 1 (±1 day) | | | | | Cycles 2–6 (±2 days) | | | | | |
| | Day 1 | Day 5 | Day 8 | Day 10 | Day 15 | Day 1 | Day 5 | Day 10 | Day 1 | Day 5 | Day 10 |
| Obinutuzumab [b] (1000 mg IV) | x | | x | | x | x | | | x | | |
| Idasanutlin [b] (PO QD) | Days 1–5 | | | | | Days 1–5 | | | TBD [c] | | |
| Venetoclax [b] (PO QD) | Days 1–5 or Days 1–10 [d] | | | | | Days 1–5 or Days 1–10 [d] | | | TBD [c] | | |

IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PO = by mouth; QD = once a day; TBD = to be determined.

[a] Total duration of consolidation is 6 months.

[b] Refer to Section 4.3.2 for instructions on study treatment administration.

[c] Regimen will be defined based on available safety, tolerability, PK, and PD data.

[d] Regimen is defined according to the dose-escalation plan (see Section 3.1.2).

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phase (cont.)

## Study Treatment Administration: Dose Escalation for the Bridging Cohorts

| Study Treatment | Induction (Six 28-Day Cycles) | | | Consolidation Every 2 Months [a] |
|---|---|---|---|---|
| | Cycles 1–6 (±1 day) | | | |
| | Day 1 | Day 5 | Day 10 | Day 1 |
| Rituximab [b] (375 mg/m$^2$ IV) | x | | | x |
| Idasanutlin [b] (PO QD) | Days 1–5 | | | TBD [c] |
| Venetoclax [b] (PO QD) | Days 1–5 or Days 1–10 [d] | | | TBD [c] |

IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PO = by mouth; QD = once a day; TBD = to be determined.

[a] Total duration of maintenance is 24 months for obinutuzumab and 6 months for idasanutlin and venetoclax.

[b] Refer to Section 4.3.2 for instructions on study treatment administration.

[c] Regimen will be defined based on available safety, tolerability, PK, and PD data.

[d] Regimen is defined according to the dose-escalation plan (see Section 3.1.2).

# Appendix 2
# Schedule of Activities for Patients with Diffuse Large B-Cell Lymphoma: Dose-Escalation and Expansion Phases (cont.)

## Study Treatment Administration: Expansion Phase

| Study Treatment | Induction (Six 28-Day Cycles) Cycles 1–6 (±1 day) Day 1 | Day 5 | Day 10 | Consolidation Every 2 Months [a] Day 1 |
|---|---|---|---|---|
| Rituximab [b] (375 mg/m$^2$ IV) | x | | | x |
| Idasanutlin [b] (PO QD) | Days 1–5 | | | TBD [c] |
| Venetoclax [b] (PO QD) | Days 1–5 or Days 1–10 [d] | | | TBD [c] |

IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; PO = by mouth; QD = once a day; TBD = to be determined.

[a] Total duration of maintenance is 24 months for obinutuzumab and 6 months for idasanutlin and venetoclax.

[b] Refer to Section 4.3.2 for instructions on study treatment administration.

[c] Regimen will be defined based on available safety, tolerability, PK, and PD data.

[d] Regimen is defined according to the dose-escalation plan (see Section 3.1.2).

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule

**Dose-Escalation Phase (Induction Treatment for FL and DLBCL Patients; 28-Day Cycles) in Regimen A**

| Study Visit | | Serum Obinutuzumab PK Sample [b] | Serum Rituximab PK Sample [a,b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|---|---|
| Cycle 1 | Day 1 [d] | Pre-infusion (any time prior to dose on that day) [e]<br>30 (±10 min) after end of infusion | Pre-infusion (any time prior to dose on that day) [e]<br>30 (±10 min) after end of infusion | Pre-administration (any time prior to dose on that day); [e]<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (any time prior to dose on that day);<br>6 hr (±20 min) post-venetoclax administration |
| | Day 5 | — | | Pre-administration (within 1 hr prior to dose);<br>2 hr (±10 min) post-idasanutlin administration;<br>4 hr (±10 min) post-idasanutlin administration;<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>2 hr (±10 min) post-venetoclax administration;<br>4 hr (±10 min) post-venetoclax administration;<br>6 hr (±20 min) post-venetoclax administration |
| Cycle 2 | Day 1 | Pre-infusion (within 5 hr prior to dose)<br>30 (±10) min after end of infusion | Pre-infusion (within 5 hr prior to dose) | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-venetoclax administration; |

ADA = anti-drug antibody; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HACA = human anti–chimeric antibody; HAHA = human anti-human antibody; PK = pharmacokinetic. Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.

[b] Samples collected for PK analysis may be used for additional PK, HAHA, HACA, and/or ADA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.

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

[e] The Day 1, Cycle 1 predose PK sample may be taken any time prior to the first dose that day.

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Dose-Escalation Phase (Induction Treatment for FL and DLBCL Patients; 28-Day Cycles) in Regimen A (cont.)**

| Study Visit | | Serum Obinutuzumab PK Sample [b] | Serum Rituximab PK Sample [a, b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|---|---|
| Cycle 2 (cont.) | Day 5 | — | | Pre-administration (within 1 hr prior to dose);<br>6 (±20 min) hr post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-venetoclax administration |
| Cycle 4 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (±10) min after the end of infusion | Pre-infusion (within 5 hr prior to dose) | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-venetoclax administration |
| | Day 5 | — | | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (± 20 min) post-venetoclax administration |
| Cycle 6 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (±10) min after the end of infusion | Pre-infusion (within 5 hr prior to dose);<br>30 (±10) min after the end of infusion | — | — |

ADA = anti-drug antibody; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HACA = human anti–chimeric antibody; HAHA = human anti-human antibody; PK = pharmacokinetic. Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.

[b] Samples collected for PK analysis may be used for additional PK, HAHA, HACA, and/or ADA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.

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

[e] The Day 1, Cycle 1 predose PK sample may be taken any time prior to the first dose that day.

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Expansion Phase (Induction Treatment for FL and DLBCL Patients; 28-Day Cycles) in Regimen A**

| Study Visit | | Serum Obinutuzumab PK Sample [b] | Serum Rituximab PK Sample [a, b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|---|---|
| Cycle 1 | Day 1 [d] | Pre-infusion (any time prior to dose on that day); [e]<br>30 (±10) min after the end of infusion | Pre-infusion (any time prior to dose on that day); [e]<br>30 (±10) min after the end of infusion | Pre-administration (any time prior to dose on that day);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (any time prior to dose on that day);<br>6 hr (±20 min) post-venetoclax administration |
| | Day 5 | — | | Pre-administration (within 1 hr prior to dose);<br>2 hr (±10 min) post-idasanutlin administration;<br>4 hr (±10 min) post-idasanutlin administration;<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>2 hr (±10 min) post-venetoclax administration;<br>4 hr (±10 min) post-venetoclax administration;<br>6 hr (±20 min) post-venetoclax administration |
| Cycle 2 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (±10 min) after the end of infusion | Pre-infusion (within 5 hr prior to dose) | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-venetoclax administration |

ADA = anti-drug antibody; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HACA = human anti–chimeric antibody; HAHA = human anti-human antibody; PK = pharmacokinetic. Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.

[b] Samples collected for PK analysis may be used for additional PK, HAHA, HACA, and/or ADA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.

[d] The Day 1, Cycle 1 predose PK sample may be taken any time prior to the first dose that day.

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

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Expansion Phase (Induction Treatment for FL and DLBCL Patients; 28-Day Cycles) in Regimen A (cont.)**

| Study Visit | | Serum Obinutuzumab PK Sample [b] | Serum Rituximab PK Sample [a, b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|---|---|
| Cycle 2 (cont.) | Day 5 | — | | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-venetoclax administration |
| Cycle 4 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (±10) min after the end of infusion | Pre-infusion (within 5 hr prior to dose) | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-venetoclax administration |
| | Day 5 | — | | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-venetoclax administration |
| Cycle 6 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (±10) min after the end of infusion | Pre-infusion (within 5 hr prior to dose);<br>30 (±10) min after the end of infusion | — | — |

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; PK = pharmacokinetic.
Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.
[b] Samples collected for PK analysis may be used for additional PK, HAHA, HACA, and/or ATA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.
[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.
[d] The Day 1, Cycle 1 predose PK sample may be taken any time prior to the first dose that day.
[e] If the Day 1, Cycle 1 dose of obinutuzumab or rituximab is split over 2 days, take the 30 minutes post-infusion obinutuzumab or rituximab PK sample relative to the end of the infusion on Day 2, and ensure that the date and time of the PK collection are accurately recorded.

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Dose-Escalation Phase (Induction Treatment for FL Patients; 28-Day Cycles) In Regimen B**

| Study Visit | | Serum Obinutuzumab PK Sample [a, b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|---|
| Cycle 1 | Day 1 [d] | Pre-infusion (any time prior to dose on that day); [e]<br>30 (±10 min) after end of infusion | Pre-administration (any time prior to dose on that day) [e] | Pre-administration (any time prior to dose on that day) |
| | Day 5 | — | — | — |
| Cycle 2 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (±10) min after end of infusion | Pre-administration (any time prior to dose on that day);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (any time prior to dose on that day);<br>6 hr (±20 min) post-venetoclax administration |

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; PK = pharmacokinetic.

Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.

[b] Samples collected for PK analysis may be used for additional PK, HAHA, and/or ATA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.

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

[e] The Day 1, Cycle 1 predose PK sample may be taken any time prior to the first dose that day.

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Dose-Escalation Phase (Induction Treatment for FL Patients; 28-Day Cycles) in Regimen B (cont.)**

| Study Visit | | Serum Obinutuzumab PK Sample [a, b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|---|
| Cycle 2 (cont.) | Day 5 | — | Pre-administration (within 1 hr prior to dose);<br>Pre-administration (within 1 hr prior to dose);<br>2 hr (±10 min) post-idasanutlin administration;<br>4 hr (±10 min) post-idasanutlin administration;<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>2 hr (±10 min) post-venetoclax administration;<br>4 hr (±10 min) post-venetoclax administration;<br>6 hr (±20 min) post-venetoclax administration |
| Cycle 4 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (±10) min after the end of infusion | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-venetoclax administration |
| | Day 5 | — | Pre-administration (within 1 hr prior to dose);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (± 20 min) post-venetoclax administration |
| Cycle 6 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (±10) min after the end of infusion | — | — |

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; PK = pharmacokinetic.

Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.

[b] Samples collected for PK analysis may be used for additional PK, HAHA, and/or ATA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Dose-Escalation Phase (Induction Treatment for FL Patients; 28-Day Cycles) in Regimen B (cont.)**

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

[e] The Day 1, Cycle 1 predose PK sample may be taken any time prior to the first dose that day.

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Expansion Phase (Induction Treatment for FL Patients; 28-Day Cycles) in Regimen B**

| Study Visit | | Serum Obinutuzumab PK Sample [a, b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|---|
| Cycle 1 | Day 1 [d] | Pre-infusion (any time prior to dose on that day); [e]<br>30 (±10) min after the end of infusion | Pre-administration (any time prior to dose on that day) | Pre-administration (any time prior to dose on that day) |
| | Day 5 | — | — | — |
| Cycle 2 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (±10 min) after the end of infusion | Pre-administration (any time prior to dose on that day);<br>6 hr (±20 min) post-idasanutlin administration | Pre-administration (any time prior to dose on that day);<br>6 hr (±20 min) post-venetoclax administration |

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; PK = pharmacokinetic.

Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.

[b] Samples collected for PK analysis may be used for additional PK, HAHA, and/or ATA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.

[d] The Day 1, Cycle 1 predose PK sample may be taken any time prior to the first dose that day.

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

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Expansion Phase (Induction Treatment for FL Patients; 28-Day Cycles) in Regimen B (cont.)**

| Study Visit | | Serum Obinutuzumab PK Sample [a, b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|---|
| Cycle 2 (cont.) | Day 5 | — | Pre-administration (within 1 hr prior to dose);<br>2 hr (± 10 min) post-idasanutlin administration;<br>4 hr (± 10 min) post-idasanutlin administration;<br>6 hr (± 20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>2 hr (± 10 min) post-venetoclax administration;<br>4 hr (± 10 min) post-venetoclax administration;<br>6 hr (± 20 min) post-venetoclax administration |
| Cycle 4 | Day 1 | Pre-infusion (within 5 hr prior to dose);<br>30 (± 10) min after the end of infusion | Pre-administration (within 1 hr prior to dose);<br>6 hr (± 20 min) post-idasanutlin administration | Pre-administration<br>(within 1 hr prior to dose);<br>6 hr (± 20 min) post-venetoclax administration |
| | Day 5 | — | Pre-administration (within 1 hr prior to dose);<br>6 hr (± 20 min) post-idasanutlin administration | Pre-administration (within 1 hr prior to dose);<br>6 hr (± 20 min) post-venetoclax administration |
| Cycle 6 | Day 1 | Pre-infusion<br>(within 5 hr prior to dose);<br>30 (± 10) min after the end of infusion | — | — |

DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; PK = pharmacokinetic.
Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.
[b] Samples collected for PK analysis may be used for additional PK, HACA, and/or ATA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.
[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.
[d] The Day 1, Cycle 1 predose PK sample may be taken any time prior to the first dose that day.
[e] If the Day 1, Cycle 1 dose of obinutuzumab is split over 2 days, take the 30 minutes post-infusion obinutuzumab PK sample relative to the end of the infusion on Day 2, and ensure that the date and time of the PK collection are accurately recorded.

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Post-Induction Treatment (Eligible FL Patients)**

| Study Visit | Serum Obinutuzumab PK Sample [a, b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|
| Month 1, Day 1 | Pre-infusion (within 5 hr prior to dose) | — | — |
| Month 7, Day 1 | Pre-infusion (within 5 hr prior to dose) | — | — |
| Month 13, Day 1 | Pre-infusion (within 5 hr prior to dose) | — | — |
| Month 19, Day 1 | Pre-infusion (within 5 hr prior to dose) | — | — |
| Post-treatment | — | — | — |
| Treatment discontinuation | Any time during visit | — | — |
| 120 days after the last dose | Any time during visit | — | — |
| 1–2 years after the last dose | Any time during visit (if patient is in the clinic) | — | — |

FL = follicular lymphoma; PK = pharmacokinetic.

Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.

[b] Samples collected for PK analysis may be used for additional PK, HAHA, and/or ATA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.

# Appendix 3
# Pharmacokinetic and Biomarker Sampling Schedule (cont.)

**Post-Induction Treatment (Eligible DLBCL Patients)**

| Study Visit | Serum Rituximab PK Sample [a, b] | Plasma Idasanutlin PK and Serum MIC-1 Sample [c] | Plasma Venetoclax PK Sample |
|---|---|---|---|
| Post-treatment | — | — | — |
| Treatment discontinuation | Any time during visit | — | — |
| 120 days after the last dose | Any time during visit | — | — |
| 1–2 years after the last dose | Any time during visit (if patient is in the clinic) | — | — |

DLBCL = diffuse large B-cell lymphoma; PK = pharmacokinetic.

Note: A "—" indicates not applicable.

[a] Sample collection timing is relative to the specified drug.

[b] Samples collected for PK analysis may be used for additional PK, HACA, and/or ATA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.

[c] Two tubes for plasma and serum, respectively, at each sampling timepoint.

# Appendix 4
# Lugano Response Criteria for Malignant Lymphoma
# (Cheson et al. 2014)

In this study, the designation of a complete response (CR) using positron emission tomography–computed tomography (PET-CT)–based response requires normal bone marrow by morphology for patients with bone marrow involvement at baseline. If indeterminate by morphology, immunohistochemistry must be negative. Additionally, designation of PET-CT−based partial response (PR) requires that computed tomography (CT)-based response criteria for a CR or a PR be met in addition to the PET-CT− based response criteria for a PR.

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET-CT–Based Response | CT-Based Response |
| Complete | Complete metabolic response | Complete radiologic response (all of the following) |
| Lymph nodes and extralymphatic sites | Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b]<br>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<br>No extralymphatic sites of disease |
| Non-measured lesion | Not applicable | Absent |
| Organ enlargement | Not applicable | Regress to normal |
| New lesions | None | None |
| Bone marrow | No evidence of FDG-avid disease in marrow | Normal by morphology; if indeterminate, IHC negative |

# Appendix 4
# Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET-CT–Based Response | CT-Based Response |
| Partial | Partial metabolic response | Partial remission (all of the following) |
| Lymph nodes and extralymphatic sites | Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size | ≥ 50% decrease in the sum of the product of the diameters SPD of up to 6 target measurable nodes and extranodal sites |
| | At interim, these findings suggest responding disease | When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value |
| | At end of treatment, these findings indicate residual disease | When no longer visible, 0 × 0 mm |
| | | For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation |
| Non-measured lesion | Not applicable | Absent/normal, regressed, but no increase |
| Organ enlargement | Not applicable | Spleen must have regressed by > 50% in length beyond normal |
| New lesions | None | None |
| Bone marrow | Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan. | Not applicable |

# Appendix 4
# Lugano Response Criteria for Malignant Lymphoma
# (Cheson et al. 2014) (cont.)

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET-CT–Based Response | CT-Based Response |
| No response or stable disease | No metabolic response | Stable disease |
| Target nodes/nodal masses, extranodal lesions | Score 4 or 5 [b] with no significant change in FDG uptake from baseline at interim or end of treatment | < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met |
| Non-measured lesion | Not applicable | No increase consistent with progression |
| Organ enlargement | Not applicable | No increase consistent with progression |
| New lesions | None | None |
| Bone marrow | No change from baseline | Not applicable |

# Appendix 4
# Lugano Response Criteria for Malignant Lymphoma
# (Cheson et al. 2014) (cont.)

| Revised Criteria for Response Assessment | | |
|---|---|---|
| Response and Site | PET-CT–Based Response | CT-Based Response |
| Progressive disease | Progressive metabolic disease | Progressive disease requires at least 1 of the following |
| Individual target nodes/nodal masses | Score 4 or 5 [b] with an increase in intensity of uptake from baseline and/or | PPD progression: |
| Extranodal lesions | New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment | An individual node/lesion must be abnormal with:<br>LDi > 1.5 cm and<br>Increase by ≥ 50% from PPD nadir and<br>An increase in LDi or SDi from nadir<br>0.5 cm for lesions ≤ 2 cm<br>1.0 cm for lesions > 2 cm<br>In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline.<br>New or recurrent splenomegaly<br>New or clear progression of preexisting non-measured lesions |
| 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<br>A new node > 1.5 cm in any axis<br>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<br>Assessable disease of any size unequivocally attributable to lymphoma |
| Bone marrow | New or recurrent FDG-avid foci | New or recurrent involvement |

# Appendix 4
# Lugano Response Criteria for Malignant Lymphoma
# (Cheson et al. 2014) (cont.)

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

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

[b] PET 5PS: 1 = no uptake above background; 2 = uptake $\leq$ mediastinum; 3 = uptake $>$ mediastinum but $\leq$ 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
## Classification of Tumor Lysis Syndrome Based on Howard Definition

To qualify for laboratory tumor lysis syndrome (TLS), a patient must have two or more metabolic abnormalities as defined in Table 1 during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward (TLS risk decreases along treatment cycles). To qualify for clinical TLS, a patient must qualify for laboratory tumor lysis syndrome and have clinical signs of hyperkalemia, hypocalcemia, or acute kidney injury, such as (but not limited to) oliguria, increased creatinine, seizures, cardiac dysrhythmia, or death.

### Table 1 Criteria for Classification of Laboratory and Clinical Tumor Lysis Syndrome

| Metabolic Abnormality | Criteria for Classification of Laboratory Tumor Lysis Syndrome [a] | Criteria for Classification of Clinical Tumor Lysis Syndrome [b] |
|---|---|---|
| Hyperuricemia | Uric acid $>$ 8.0 mg/dL (475.8 μmol/L) in adults or above the upper limit of the normal range for age in children | Not applicable |
| Hyperphosphatemia | Phosphorus $>$ 4.5 mg/dL (1.5 μmol/L) in adults or $>$ 6.5 mg/dL (2.1 μmol/L) in children | Not applicable |
| Hyperkalemia | Potassium $>$ 6.0 μmol/L | Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia |
| Hypocalcemia | Corrected calcium $<$ 7.0 mg/dL (1.75 μmol/L) or ionized calcium $<$ 1.12 (0.3 μmol/L) [c] | Cardiac dysrhythmia, sudden death, seizures, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia |
| Acute kidney injury [c] | Not applicable | Increase from baseline creatinine of $\geq$ 0.3 mg/dL (26.5 μmol/L), anuria, oliguria (defined as an average urine output of $<$ 0.5 mL/kg/hr for 6 hours or more), or other clinical symptoms indicative of acute kidney injury |

Source: Howard SC, Jones P, Pui CH. The tumor lysis syndrome. N Engl J Med 2011:12;364:1844–54.

[a] To qualify for laboratory tumor lysis syndrome, a patient must have two or more metabolic abnormalities during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward.

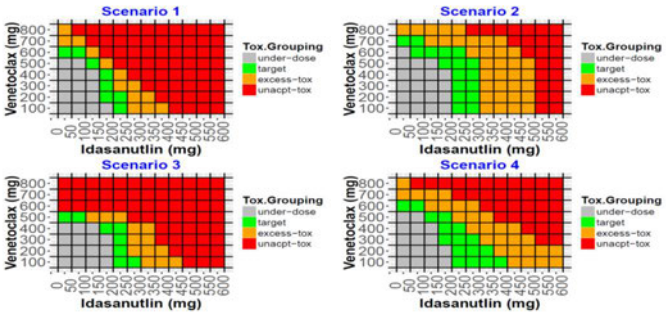
[b] To qualify for clinical tumor lysis syndrome, a patient must qualify for laboratory tumor lysis syndrome and have clinical signs of hyperkalemia, hypocalcemia, or acute kidney injury, such as (but not limited to) oliguria, increased creatinine, seizures, cardiac dysrhythmia, or death.

[c] Corrected calcium (mg/dL) = measured calcium (mg/dL) + 0.8 × (4 − albumin [g/dL]).

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control

In order to evaluate the operating characteristics of the modified Continual Reassessment Model (mCRM), simulations were performed under four different true scenarios, with each scenario describing the true relationship between dose-limiting toxicity (DLT) rate and dose combinations of idasanutlin and venetoclax (see Figure 1).

**Figure 1 True Scenarios Describing the Toxicity of Each Combination of Idasanutlin and Venetoclax**




The parameters of the mCRM corresponding to the four scenarios are presented in Table 1. In the first two scenarios, the true value for each parameter is set to the mean value of the corresponding prior distribution (prior), with the exception of $\gamma$, for which Scenario 1 assumes $\gamma = 0$ (no interaction between idasanutlin and venetoclax) and Scenario 2 assumes $\gamma = 1.0$ (synergistic interaction). Scenarios 3 and 4, in which the value of $\gamma$ is set to 0.5, consider cases in which the slope of the marginal logistic model signifies that venetoclax is more toxic than the prior assumption (Scenario 3) or that idasanutlin is less toxic than the prior assumption (Scenario 4).

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

**Table 1: Parameters of the mCRM Corresponding to Different Scenarios**

| Scenario | $\alpha_1$ | $\alpha_2$ | $\beta_1$ | $\beta_2$ | $\gamma$ |
|---|---|---|---|---|---|
| 1 | −2.0 | −3.9 | 2.5 | 5.4 | 1.0 |
| 2 | −2.0 | −3.9 | 2.5 | 5.4 | 0.0 |
| 3 | −2.0 | −3.9 | 2.5 | 11.0 | 0.5 |
| 4 | −2.0 | −3.9 | 1.3 | 5.4 | 0.5 |

mCRM = modified Continual Reassessment Model.

The following possible dose levels were considered for idasanutlin (to be given in combination with venetoclax): 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, and 600 mg. The following possible dose levels were considered for venetoclax (to be given in combination with idasanutlin): 100, 200, 300, 400, 500, 600, 700, and 800 mg.

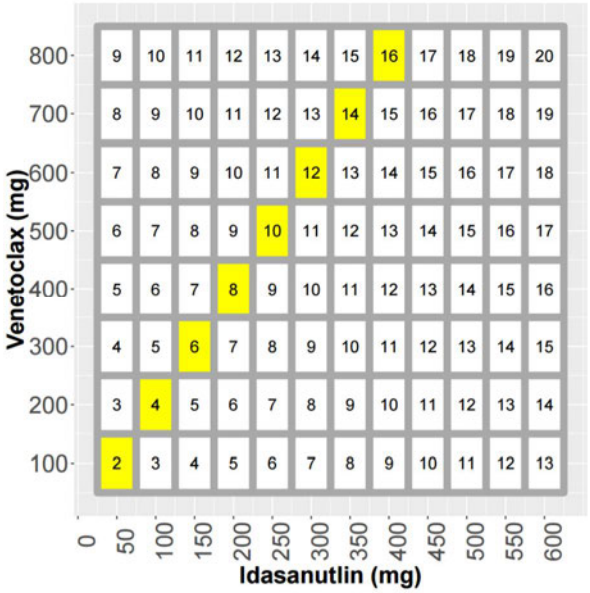
For each scenario, 1000 simulations were performed, with each simulation mimicking a complete dose-escalation study outcome.

A fixed sample size of 42 patients (14 cohorts of 3 patients each) was considered, with the possibility of dosing for up to a maximum of two cohorts in parallel.

All possible combinations of doses to be potentially explored in the simulations and in this study are shown Figure 2, in which a grid score (in this case, a number ranging from 2 to 20) is reported for each combination and represents how far the corresponding combination lies from the origin (the left bottom corner).

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

## Figure 2 All Possible Dose Combinations of Idasanutlin and Venetoclax




The starting dose combination for each simulation was 100 mg for idasanutlin and 200 mg for venetoclax. Dose combinations for subsequent cohorts were selected using the algorithm described below:

1. The following terms are represented in the algorithm:
   - $I_{max}$ and $V_{max}$ are the maximum doses for idasanutlin (I) and venetoclax (V), respectively, from all dose combinations already tested (e.g., if only the first cohort had been tested, $I_{max} = 100$ mg and $V_{max} = 200$ mg)
   - [I, V] is one of the possible idasanutlin and venetoclax dose combinations for the next cohort(s)
2. The mCRM is updated with information on DLTs from all cohorts (dose combinations) already tested

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

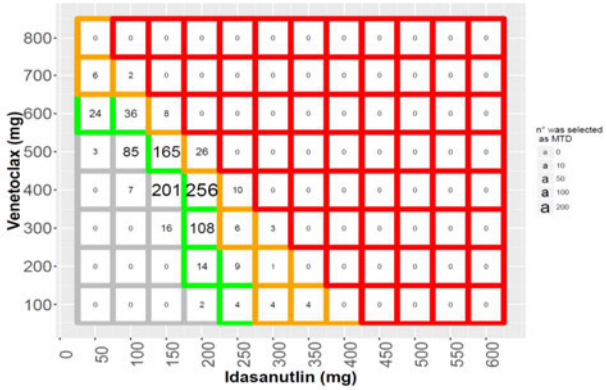
3. From all possible combinations of doses [I, V], only those fulfilling the following criteria are further considered as potential dose(s) for the next cohort(s):
   a) The probability of having a DLT rate of $>33\%$ is $<35\%$
   b) The grid score is not above the maximum grid score (across all dose combinations already tested) plus 2 (e.g., the starting dose for the simulations had a grid score of 4; thus, the next dose combination had to have a grid score of $\leq 6$)
   c) $I \leq I_{max}$ <u>or</u> $V \leq V_{max}$ (which means that only one of the doses can be higher than the maximum dose already tested for that drug)
   d) $I \leq I_{max} + 100$ mg <u>and</u> $V \leq V_{max} + 200$ mg (which means that only 100-mg and 200-mg increments are allowed above the maximum dose already tested for idasanutlin and venetoclax, respectively)
4. Among the remaining dose combinations, only those with the maximum grid score are considered further (referred to as "Set" Ω) and the next dose combination(s) are chosen among Ω as described below:
   a) If Ω was composed of one dose combination, this is selected as the dose combination for the next cohort of 3 patients.
   b) If Ω is composed of two or more dose combinations, the next dose combination(s) are chosen as follows:
      - If one of the dose combinations in Ω is located on the diagonal (highlighted in yellow in Figure 2) and has not been tested before, this is selected as the dose combination for the next cohort of 3 patients.
      - Otherwise, the two dose combinations in Ω with the highest probability of being within the target toxicity interval are selected to be tested in parallel in the next two cohorts of 3 patients.

Each simulation was stopped once 14 cohorts of 3 patients were tested and the outcome was the predicted maximum tolerated dose (MTD; one or a maximum of two dose combinations), obtained using the algorithm described above for selection of the next dose.

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

Results of the simulations for the different scenarios are reported in Figures 3, 4, 5, and 6 (for Scenarios 1, 2, 3, and 4, respectively), as well as in Table 2. The figures show the number of times each dose combination was predicted to be the MTD (after all 14 cohorts were tested) across the 1000 simulations. If the algorithm suggested two dose combinations as the MTD, only the combination with the highest probability of being within the target toxicity interval, as predicted by the model, was used in these plots. The true toxicity at each dose combination for the corresponding true scenario is overlaid on each plot, allowing the figures to clearly capture the performance of the mCRM.

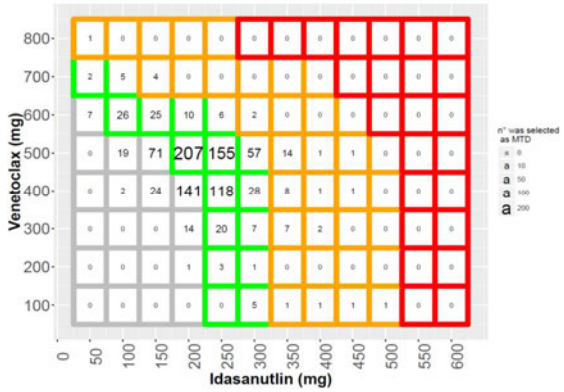
## Figure 3 Number of Times Each Dose Combination Was Selected as MTD for Scenario 1




MTD = maximum tolerated dose.

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

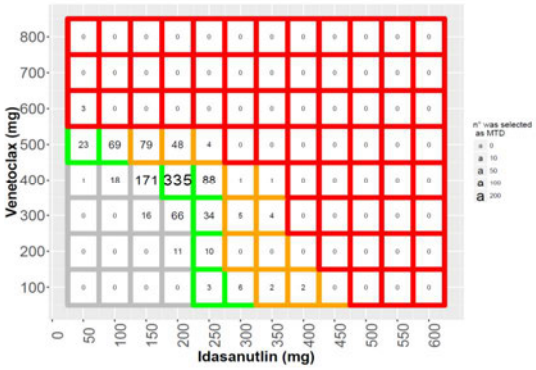
## Figure 4 Number of Times Each Dose Combination Was Selected as MTD for Scenario 2




MTD = maximum tolerated dose.

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

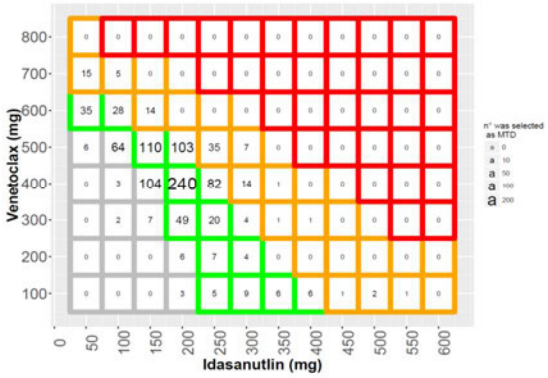
## Figure 5 Number of Times Each Dose Combination Was Selected as MTD for Scenario 3




MTD = maximum tolerated dose.

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

## Figure 6 Number of Times Each Dose Combination Was Selected as MTD for Scenario 4




MTD = maximum tolerated dose.

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

Table 2 shows the following information for each scenario across the 1000 simulations:

- The percentage of times (out of 1000) the "best" model-predicted MTD (the combination with the highest probability of achieving the target toxicity interval [DLT rate of 16%–33%] in case two dose combinations were predicted as the MTD) had true toxicity within the target toxicity interval
- The percentage of times either of the two model-predicted MTDs (in case two dose combinations were predicted as the MTD) had true toxicity within the target toxicity interval
- The median number of patients (together with 10th and 90th percentiles) who received a dose combination for which the true toxicity was above the target toxicity interval (DLT rate > 33%; overdosing)
- The median number of patients (together with 10th and 90th percentiles) who received a dose combination for which the true toxicity was unacceptable (DLT rate > 60%).

**Table 2: mCRM Design across the Different Scenarios**

| Scenario | Percentage of Times the Best MTD Was Truly in the Target Toxicity Range | Percentage of Times at Least One of the Best Two MTDs Was Truly in the Target Toxicity Range | No. of Patients Who Were Treated Above the Target Toxicity Interval (Median [10th, 90th Percentiles] | No. of Patients Who Were Treated at Unacceptable Toxicity (Median [10th, 90th Percentiles] |
|---|---|---|---|---|
| 1 | 62% | 81% | 0 [0, 12] | 0 [0, 0] |
| 2 | 67% | 81% | 0 [0, 3] | 0 [0, 0] |
| 3 | 56% | 83% | 6 [0, 15] | 0 [0, 3] |
| 4 | 70% | 84% | 0 [0, 9] | 0 [0, 0] |

mCRM = modified Continual Reassessment Model; MTD = maximum tolerated dose.

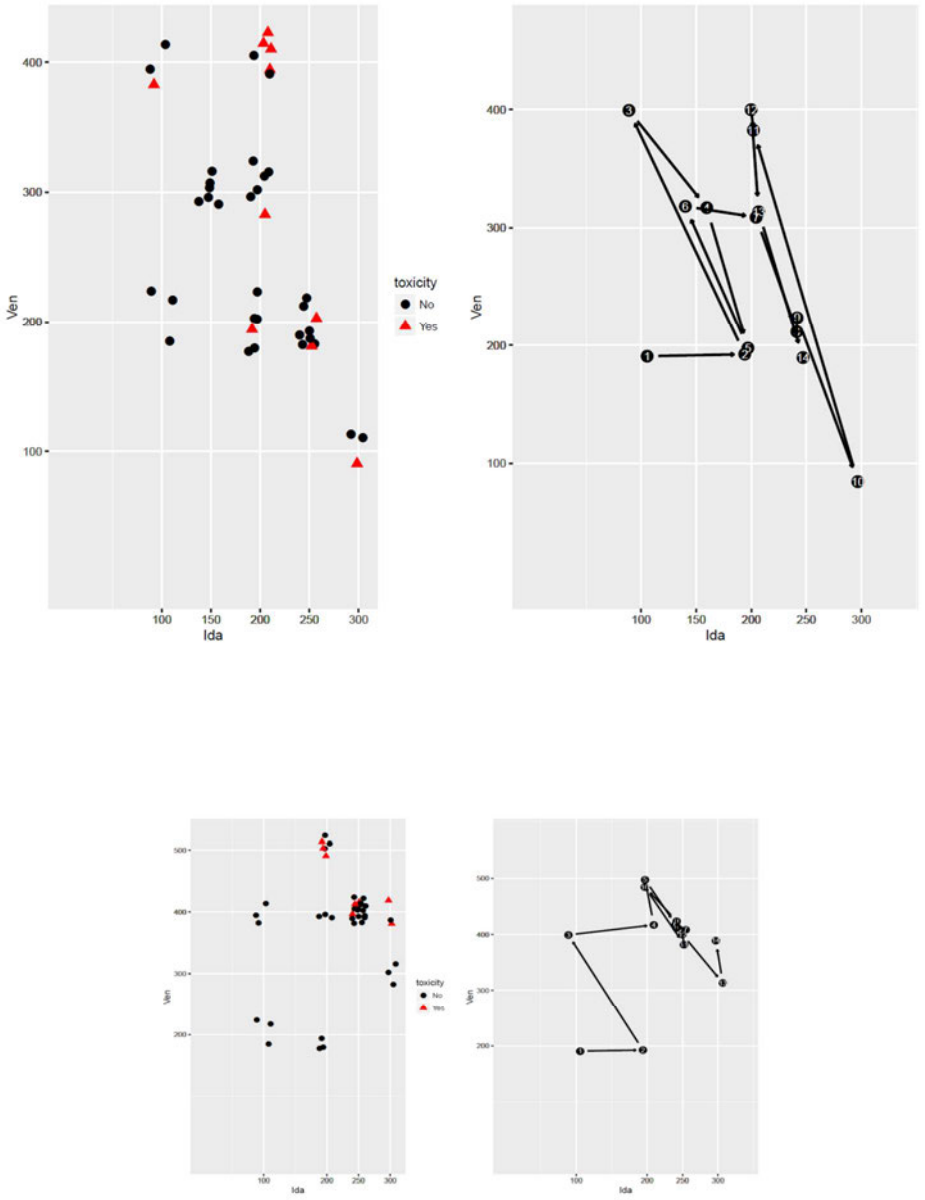
# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

Figures 7, 8, 9, and 10 show for Scenarios 1, 2, 3, and 4, respectively, two examples (from the simulations) of how a complete dose escalation (with up to 42 patients) would occur using the proposed mCRM.

As indicated by the results shown in Figures 7, 8, 9, and 10, it can be concluded that the proposed mCRM provides overall very good performance in selecting the correct MTD, while at the same time limiting the amount of overdosing across all scenarios, with the assumed sample size of 42 patients.

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

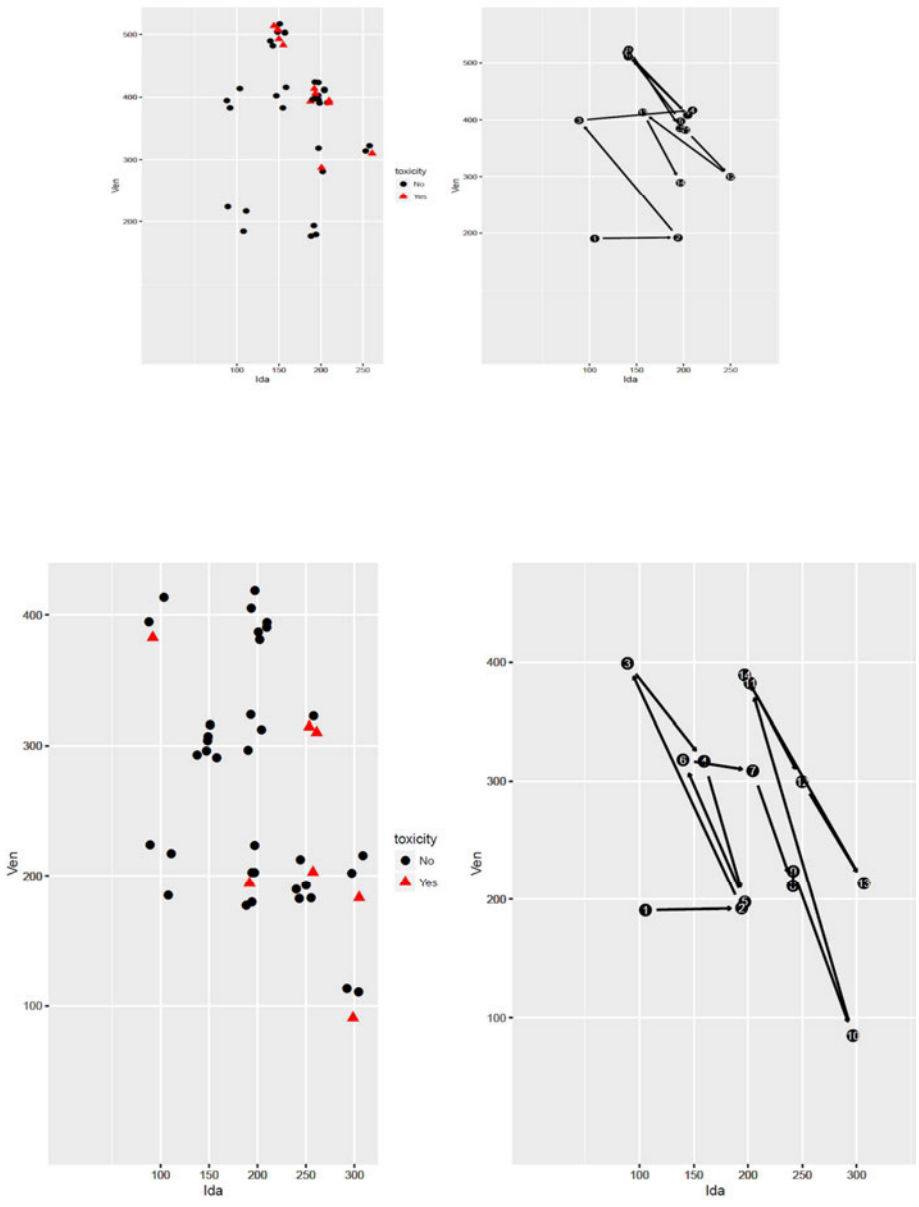
## Figure 7 Example of Two Complete Trial Realizations in Scenario 1




Ida = idasanutlin; Ven = venetoclax.
Note: Random noise was added to the data along both axis to allow seeing points that otherwise would have overlapped.

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

## Figure 8 Example of Two Complete Trial Realizations in Scenario 2

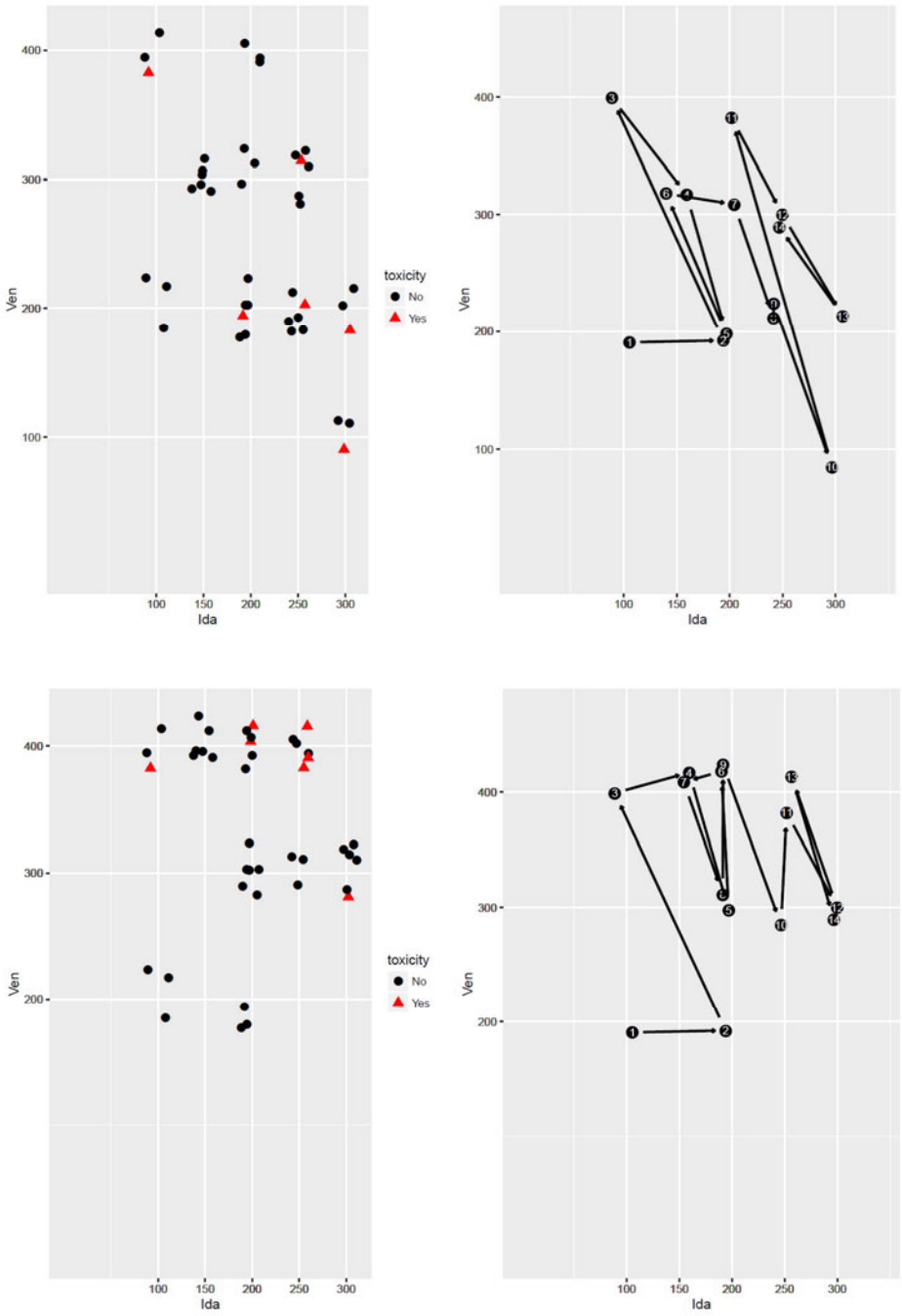



Ida = idasanutlin; Ven = venetoclax.

Note: Random noise was added to the data along both axis to allow seeing points that otherwise would have overlapped.

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

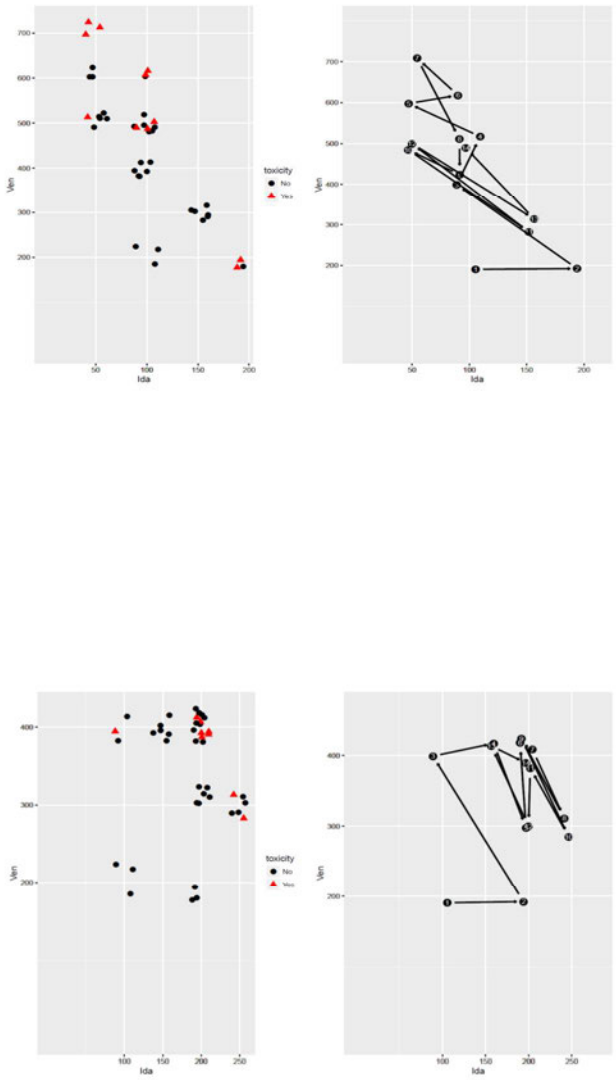
## Figure 9 Example of Two Complete Trial Realizations in Scenario 3




Ida = idasanutlin; Ven = venetoclax.
Note: Random noise was added to the data along both axis to allow seeing points that otherwise would have overlapped.

# Appendix 6
# Operating Characteristics of the Modified Continual Reassessment Model for Dose Escalation with Overdose Control (cont.)

## Figure 10 Example of Two Complete Trial Realizations in Scenario 4




Ida = idasanutlin; Ven = venetoclax.

Note: Random noise was added to the data along both axes to allow visibility of points that otherwise would have overlapped.

# Appendix 7
# ECOG Performance Status Scale

| Grade | Description |
|---|---|
| 0 | Fully active; able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work). |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about $>$ 50% of waking hours. |
| 3 | Capable of only limited self-care; confined to a bed or chair $>$ 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

# Appendix 8
# Ann Arbor Staging

| Grade | Description |
|---|---|
| Stage I | Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE) [a] |
| Stage II | Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE) |
| Stage III | Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIIES) |
| Stage IV [b] | Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement |

Note: All cases are subclassified to indicate the absence (A) or presence (B) of the systemic B symptoms of significant unexplained fever (>38°C), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

[a] The designation "E" generally refers to extranodal contiguous extension (i.e., proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. A single extralymphatic site as the only site of disease should be classified as IE, rather than Stage IV.

[b] Involvement of bone marrow at screening will always qualify for Ann Arbor Stage IV and should be recorded as extranodal involvement.

Adapted from:

Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860–1.

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds Meeting. J Clin Oncol 1989;7:1630–6.

# Appendix 9
# Follicular Lymphoma International Prognostic Index and International Prognostic Index

## Table 1 Follicular Lymphoma International Prognostic Index

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

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

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

Adapted from:

Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258–64.

# Appendix 9
# Follicular Lymphoma International Prognostic Index and International Prognostic Index (cont.)

## Table 2 Follicular Lymphoma International Prognostic Index 2

| FLIPI2 Risk Factor |
|---|
| Bone marrow involvement |
| Age $>60$ years |
| $\beta_2$ microglobulin $>1\times$ ULN |
| Anemia (hemoglobin $<120$ g/L) |
| Longest diameter of largest involved node $>6$ cm |

| FLIPI2 Risk Group | Number of FLIPI2 Risk Factors |
|---|---|
| Low | 0 |
| Intermediate | 1 or 2 |
| High | 3 to 5 |

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

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

Adapted from:

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

# Appendix 9
# Follicular Lymphoma International Prognostic Index and International Prognostic Index (cont.)

## Table 3 International Prognostic Index

| IPI Risk Factor |
|---|
| Ann Arbor Stage III or IV |
| Age $>60$ years |
| Serum LDH $>1\times$ ULN |
| ECOG Performance Status $\geq 2$ |
| Extranodal involvement $\geq 2$ |

| IPI Risk Group | Number of IPI Risk Factors |
|---|---|
| Low | 0 or 1 |
| Low–Intermediate | 2 |
| High–Intermediate | 3 |
| High | 4 or 5 |

ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; IPI = International Prognostic Index; PET = positron emission tomography; ULN = upper limit of normal.

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

Adapted from:

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

# Appendix 10
# Anaphylaxis Precautions

## Equipment Needed

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous , and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

## Procedures

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

- Stop the study treatment infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer glucocorticoids, antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

# Appendix 11
# Calculation of Creatinine Clearance Using the modified Cockcroft-Gault Formula

$$eCCR = (140 - Age) \times IBM\ a\ (kg) \times [0.85\ if\ female])/(72 \times serum\ creatinine\ [mg/dL])$$

Or, if serum creatinine is in micromoles per liter (μmol/L):

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

eCCR = estimated creatinine clearance; IBM = ideal body weight.

[a] IBM (kg) = ([height in cm − 154] × 0.9)] + (50 if male, 45.5 if female).

# Appendix 12
# Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax

## First Dose of Venetoclax or a Dose Increase

- Within the first 24 hours after either the first dose or a dose increase, if any of the following laboratory criteria are met, the patient should be hospitalized for monitoring and the investigator notified. No additional doses of venetoclax should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission. (according to institutional standards to ensure emergency dialysis is available).
- Intravenous fluids (e.g., D5 ½ normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target: 150−200 mL/hr; not < 50 mL/hr).
- Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitoring for symptoms or signs of tumor lysis syndrome (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures)

  If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour immediately.
- Vital signs should be measured at time of all blood draws or any intervention.

The management recommendations in the following table focus on the minimal initial responses required. If a diagnosis of tumor lysis syndrome is established, ongoing intensive monitoring and multidisciplinary management will be followed according to institutional protocols.

# Appendix 12
# Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax (cont.)

| Abnormality | Management Recommendations |
|---|---|
| Hyperkalemia (including rapidly rising potassium) | |
| Potassium greater than the ULN | • Perform ECG immediately and commence telemetry.<br>• Perform nephrology assessment with consideration of initiating dialysis.<br>• Administer Kayexalate® 60 g (or Resonium A® 60 g).<br>• Administer furosemide 20 mg IV × 1.<br>• Administer calcium gluconate 100–200 mg/kg IV slowly if there is ECG or telemetry evidence of life-threatening arrhythmias.<br>• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.<br>• If potassium is less than the ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later if no other evidence of tumor lysis. |
| Potassium ≥ 0.5 μmol/L increase from prior value (even if potassium is WNL) | • Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. If there is a further increase ≥ 0.2 μmol/L in potassium, but still less than the ULN, manage per potassium greater than the ULN. Otherwise, recheck in 1 hour.<br>• Resume per protocol testing if change in potassium is < 0.2 μmol/L and potassium is less than the ULN and no other evidence of tumor lysis.<br>• At the discretion of the investigator, may recheck before hospitalization. If potassium is stable or decreased and still WNL, hospitalization will be at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours. |

ECG = electrocardiogram; IV = intravenous; STAT = immediately; ULN = upper limit of normal; WNL = within normal limit.

# Appendix 12
# Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax (cont.)

| Abnormality | Management Recommendations |
|---|---|
| Hyperkalemia (including rapidly rising potassium) (cont.) | |
| Potassium ≥6.0 μmol/L (6.0 mEq/L) and/or patient is symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, and diarrhea) | • Perform STAT ECG and commence telemetry.<br>• Perform nephrology assessment with consideration of initiating dialysis.<br>• Administer Kayexalate® 60 g (or Resonium A® 60 g).<br>• Administer furosemide 20 mg IV × 1.<br>• Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV.<br>• Administer sodium bicarbonate 1–2 mEq by IV push.<br>If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation.<br>• Administer calcium gluconate 100–200 mg/kg IV slowly if there is ECG or telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate.<br>• Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour STAT. |
| Hyperuricemia | |
| Uric acid ≥8.0 mg/dL (476 μmol/L) | • Consider rasburicase (dose per institutional guidelines).<br>If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.<br>• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. |

ECG = electrocardiogram; IV = intravenous; STAT = immediately; ULN = upper limit of normal; WNL = within normal limit.

# Appendix 12
# Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax (cont.)

| Abnormality | Management Recommendations |
|---|---|
| Hyperuricemia (cont.) | |
| Uric acid ≥ 10 mg/dL (595 μmol/L)<br>**or**<br>uric acid ≥ 8.0 mg/dL (476 μmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 μmol/L) from pre-dose level | • Administer rasburicase (dose per institutional guidelines).<br>If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.<br>• Consult nephrology.<br>• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.<br>• If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis. |
| Hypocalcemia | |
| Calcium ≤ 7.0 mg/dL (1.75 μmol/L)<br>**and**<br>patient is symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias) | • Administer calcium gluconate 50–100 mg/kg IV slowly with ECG monitoring.<br>• Perform telemetry.<br>• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.<br>• If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis.<br>• Calculate corrected calcium and check ionized calcium if albumin is low. |
| Hyperphosphatemia | |
| Phosphorus ≥ 5.0 mg/dL (1.615 μmol/L) with ≥ 0.5 mg/dL (0.16 μmol/L) increase | • Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate).<br>• Notify nephrology dialysis required for phosphorus ≥ 10 mg/dL)<br>• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.<br>• If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later if no other evidence of tumor lysis. |

ECG = electrocardiogram; IV = intravenous; STAT = immediately; ULN = upper limit of normal; WNL = within normal limit.

# Appendix 12
# Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome in the Setting of Treatment with Venetoclax (cont.)

| Abnormality | Management Recommendations |
|---|---|
| Hyperphosphatemia (cont.) | |
| Creatinine | |
| Increase ≥25% from baseline | • Start or increase rate of IV fluids.<br>• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1–2 hours STAT. |

ECG = electrocardiogram; IV = intravenous; STAT = immediately; ULN = upper limit of normal; WNL = within normal limit.

## Ongoing Dosing with Venetoclax

Management of electrolyte changes from last value at >24-hour intervals after either the first dose or dose increase (e.g., 48 or 72 hours) is described below. Note: If the patient is hospitalized, no additional doses of ventoclax should be administered until resolution.

- For potassium, admit patient for any increase ≥1.0 μmol/L (1.0 mEq/L) or any level greater than the ULN.

  Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or a dose increase (see table).
- If a smaller increase in potassium is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 24 hours and confirm no evidence of tumor lysis before further venetoclax dosing.
- For uric acid, calcium, phosphorus, and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (see table).

# Appendix 13
# Safety Overview in Solid Tumor Study NP27872, Including 3 Patients with NHL

| Adverse Event | Idasanutlin MBP 100 mg QD to 1600 BID Weekly (n=48), n (%) | Idasanutlin MBP 500 mg BID to 800 BID Daily × 3 (n=48), n (%) | Idasanutlin MBP 100 mg QD to 500 BID Daily × 5 (n=34), n (%) | Idasanutlin MBP All Patients (n=86), n (%) |
|---|---|---|---|---|
| Thrombocytopenia | 7 (15) | 7 (47) | 16 (47) | 30 (32) |
| Anemia | 3 (7) | 6 (40) | 5 (15) | 14 (15) |
| Nausea | 4 (9) | 2 (13) | 4 (12) | 10 (11) |
| Diarrhea | 2 (4) | 2 (13) | 2 (6) | 6 (6) |
| Febrile neutropenia | — | 2 (13) | 4 (12) | 6 (6) |
| Decreased appetite | 2 (4) | — | 2 (6) | 4 (4) |
| Asthenia | 1 (2) | 2 (13) | — | 3 (3) |
| Leukopenia | 1 (2) | 1 (7) | 1 (3) | 3 (3) |
| Hypokalemia | 1 (2) | 1 (7) | 1 (3) | 3 (3) |
| Fatigue | 1 (2) | — | 1 (3) | 2 (2) |
| Vomiting | 1 (2) | — | 1 (3) | 2 (2) |
| Abdominal pain | — | 1 (7) | — | 1 (1) |
| Hyponatremia | 1 (2) | — | — | 1 (1) |
| Hypophosphatemia | — | — | 1 (3) | 1 (1) |
| Increased ALT | 1 (2) | — | — | 1 (1) |
| Dehydration | — | — | 1 (3) | 1 (1) |
| Pancytopenia | — | 1 (7) | — | 1 (1) |
| Decreased weight | — | — | 1 (3) | 1 (1) |
| Tinnitus | 1 (2) | — | — | 1 (1) |
| Stomatitis | 1 (2) | — | — | 1 (1) |
| Pyrexia | — | 1 (7) | — | 1 (1) |
| Pulmonary embolism | — | — | 1 (Grade 5) (3) [a] | 1 (1) |
| QT prolonged | — | — | 1 (3) | 1 (1) |

BID=twice a day; MBP = microprecipitated bulk; NHL = non-Hodgkin's lymphoma; QD = once a day.

[a] The Grade 5 event of pulmonary embolism was assessed by the investigator to be remotely related to study treatment in a patient with urothelial cancer that occurred on Day 32. The patient had concurrent thrombocytopenia (highest, Grade 4), anemia, and febrile neutropenia (highest, Grade 3) with onset on Day 29.