Official Title: **A PHASE IB/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH IDASANUTLIN IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA AND OBINUTUZUMAB OR RITUXIMAB IN COMBINATION WITH IDASANUTLIN IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA**

NCT Number: NCT02624986

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PROTOCOL

TITLE:	**A PHASE IB/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH IDASANUTLIN IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA *AND OBINUTUZUMAB* OR *RITUXIMAB IN COMBINATION WITH IDASANUTLIN IN PATIENTS WITH RELAPSED OR REFRACTORY* DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	BH29812
VERSION NUMBER:	4
EUDRACT NUMBER:	2015-002100-83
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TEST PRODUCTS:	Obinutuzumab (RO5072759) *Rituximab (RO0452294)* Idasanutlin (RO5503781)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 29 June 2015 Version 2: 14 October 2015 Version 3: 12 February 2016
DATE AMENDED:	Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory (Clinical)	02-Mar-2017 15:56:23

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

Changes to the protocol, along with a rationale for each change, are summarized below:

- Patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) will receive idasanutlin in combination with rituximab in the expansion phase and in the dose-escalation phase after the maximum tolerated dose (MTD) of idasanutlin has been identified in combination with obinutuzumab (see Section 3.1). The rationale for this change is based on results from the Phase III GOYA (BO21005) study showing that the addition of obinutuzumab to cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone (CHOP) chemotherapy in patients with previously untreated DLBCL did not improve the primary endpoint of progression-free survival compared with the standard regimen of rituximab plus CHOP chemotherapy.

  – The background (see Section 1.2), rationale (see Section 3.3), study objectives (Section 2), study design (see Section 3), eligibility criteria (see Section 4.1), and statistical plan (see Section 6) have been updated accordingly. The updated study design includes adding bridging cohort(s) with DLBCL patients in the dose-escalation phase after the MTD of idasanutlin is identified in combination with obinutuzumab. Patients in the bridging cohort will receive idasanutlin at the MTD in combination with rituximab to confirm this MTD, or further dose escalation may be explored based on safety and tolerability (see Section 3.1.2).

  – Rituximab will be provided by the Sponsor as an investigational medicinal product. This has been reflected throughout the protocol in corresponding sections. Rituximab risks have been added (see Section 5.1.2), and Section 4.3 has been updated accordingly.

- Obinutuzumab exposure data have been updated. Sections 1.2 and 1.2.2 are updated to reflect the most up-to-date information on clinical studies, based on the Obinutuzumab Investigator's Brochure, Version 11 (September 2016, clinical cutoff 4 July 2016).

- Idasanutlin data (see Sections 1.3, 1.3.3, and 5.1.3) have been updated to reflect the most up-to-date information on clinical studies, based on the Idasanutlin Investigator's Brochure, Version 9 (November 2016, cutoff 13 September 2016).

- Idasanutlin was added as post-induction treatment in the expansion phase to explore potential benefits for extended idasanutlin treatment after induction. An exploratory efficacy endpoint, complete response at end of consolidation in DLBCL patients (expansion only) whose positron emission tomography (PET) was positive at end of induction as determined by the Independent Review Committee and by the investigator on the basis of PET and computed tomography scans, was added accordingly (see Sections 2.2.3 and 6.4.3).

- Guidelines for the second and subsequent infusion of obinutuzumab (Figure 10) have been clarified (i.e., patients with no infusion-related reactions during prior infusion will receive only an analgesic/antipyretic as premedication). Table 9 has been updated accordingly.

- The classification of second malignancies has been changed from a selected adverse event to an adverse event of special interest in order to more closely monitor this adverse event (Section 5.2.3).

- Grade • 2 *Clostridium difficile* infection has been added as adverse event of special interest in Section 5.2.3.

- An alternative regimen with obinutuzumab given alone at Cycle 1, followed by obinutuzumab in combination with idasanutlin from Cycles 2 to 6, has been added during the dose-escalation phase for FL patients to explore the possibility of alleviating hematological toxicities at Cycle 1. Sections 3.1.1, 3.1.2, 3.1.3, 3.3.3, 4.2, and 4.3.2.5 have been updated accordingly, as well as Table 2, Figure 6, and Figure 11.

- The dose-limiting toxicity (DLT) definition in Section 3.1.2.1 has been modified to include any Grade 5 toxicities unless unequivocally due to the underlying malignancy or extraneous causes.

- The DLT criterion regarding thrombocytopenia has been updated such that Grade 3 or 4 thrombocytopenia of any duration is a DLT if associated with Grade ≥3 bleeding (Section 3.1.2.1). Study treatment discontinuation in Table 17 has also been updated based on this change.

- A new DLT criterion regarding changes in liver enzyme has been introduced in Section 3.1.2.1: 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 (according to Hy's Law) and will be considered a DLT.

- Sections 3.1.2.2 and 3.1.3 have been updated to allow maintenance for patients with follicular lymphoma (FL) who achieved a complete response (CR) or partial response only. Patients with FL having stable disease will not be eligible for maintenance treatment.

- Sections 3.1.2.2 and 3.1.3 have been updated to allow patients with DLBCL who achieved 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) to proceed

with hematopoietic stem cell transplantation if deemed appropriate by the investigator.

- Exclusion criteria regarding the use of strong and moderate CYP3A inhibitors, strong and moderate CYP3A inducers, and CYP2C8 and OATP1B1/3 substrates prior to study entry and during study treatment have been clarified in Section 4.1.2.

- Section 4.4.2 has been updated to give detailed guidance on prohibited and cautionary therapies and their respective washout periods.

- The dose reduction guidance has been clarified in Table 17 and Table 19.

- Table 19 has been updated to give guidance regarding liver function test criteria for patients with liver involvement.

- Appendix 3 has been updated with guidance of the allowed time window for PK sample collection.

- Section 6.7 has been updated to clearly define the interim analysis.

- Patients are allowed to be rescreened once for technical reasons, such as longer waiting time for results or study cohort on hold. Section 4.5.1 has been updated accordingly.

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.

PROTOCOL AMENDMENT, VERSION 4:
SUMMARY OF CHANGES

PROTOCOL AMENDMENT ACCEPTANCE FORM

~~Please return the signed original of this form to the Sponsor or designee. Contact details will be provided to the investigator prior to study start. Please retain a copy for your study files.~~ *Please retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor* [redacted]

PROTOCOL SYNOPSIS

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

SECTION 1.2: BACKGROUND ON OBINUTUZUMAB

Obinutuzumab (also known as GA101) is a novel glycoengineered type II anti-CD20 antibody. Compared with the type I anti-CD20 antibody, rituximab, obinutuzumab is characterized by more potent direct B-cell death induction and increased affinity for Fc•RIII receptors expressed on natural killer (NK) cells, macrophages, and monocytes, resulting in enhanced antibody-dependent ~~cellular~~ *cell-mediated* 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 use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL). Obinutuzumab is ~~currently being investigated in a large clinical program, including two head-to-head Phase III studies versus rituximab in combinations with chemotherapy in patients with previously untreated iNHL and DLBCL~~ *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, 1.3.1, and 1.4.

SECTION 1.2.2: Clinical Studies with Obinutuzumab

As of ~~2 July 2014~~ *4 July 2016*, clinical data from Roche-sponsored studies on obinutuzumab are available from ~~eight~~*13 clinical studies: 8* Phase I or II studies (BO20999, BO21003, JO21900, BO21000, GAO4915g, GAO4779g, YP25623, and GAO4768g) and ~~two~~*5* Phase III/IIIb studies (BO21004*/CLL11, GAO4753g, MO28543, BO21223,* and ~~GAO4915g) in patients with NHL or CLL.~~*BO21005).* Available efficacy

results from the NHL cohorts in these studies and available safety results from all patients are summarized below.

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

A Phase III study (GAO4753g) investigated obinutuzumab plus bendamustine (GB) compared with bendamustine alone in patients with rituximab-refractory iNHL (n=396). Patients in the GB group who had not experienced disease progression at the end of induction received obinutuzumab monotherapy every 2 months for up to 2 years. On the basis of positive results from this study, demonstrating significant improvement in PFS in the GB arm with a median PFS of 29 versus 14 months (hazard ratio [HR], 0.52; 95% CI 0.39, 0.70; p>0.0001) (Sehn 2015), ~~the Independent Data Monitoring Committee recommended that the study be unblinded to the Sponsor~~, *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 iNHL (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 4) to cease evaluating obinutuzumab in patients with R/R DLBCL in the expansion phase. Patients with DLBCL enrolled after the identification of the idasanutlin maximum tolerated dose (MTD) in combination with obinutuzumab will instead receive idasanutlin in combination with rituximab.

SECTION 1.2.2.2: Clinical Safety of Obinutuzumab

As of the safety data cutoff date of ~~31 October 2014~~*4 July 2016*, an estimated ~~3,284~~*4454* patients with CLL or NHL had 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.

SECTION 1.3: BACKGROUND ON IDASANUTLIN

Figure 1: Regulation of p53 Stability and Activity by MDM2

The figure has been replaced with an updated schematic.

SECTION 1.3.1: Nonclinical Experience with Idasanutlin and Obinutuzumab *or Rituximab*

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.

The majority of B-lymphoid malignancies, including NHL and CLL, also express wild-type p53 (Imamura et al. 1994). The non-overlapping and complementary mechanisms of action of obinutuzumab *or rituximab* (direct tumor cell death) and idasanutlin (increased apoptosis) may provide superior efficacy in treating B-lymphoid malignancies.

In in vitro assays, idasanutlin induced concentration-dependent apoptosis in a mantle cell lymphoma cell line (Z-138) and in a diffuse large B-cell lymphoma cell line (DOHH-2), and the combination with obinutuzumab further enhanced cell death induction. Importantly, idasanutlin neither influenced obinutuzumab- *or 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-mediated NK cell activation (Herting et al. 2014; Herting et al. 2016).

In an additional in vivo study using the DoHH-2 DLBCL xenograft model, the combination of obinutuzumab *or rituximab* and idasanutlin also resulted in superior efficacy: 94% TGI using a suboptimal dose of obinutuzumab and tumor regression (TGI >100%) using 10 mg/kg of obinutuzumab *and 94% TGI using 10 mg/kg of rituximab* versus the respective monotherapy treatments (see Figure 4).

~~Although cross reactivity of idasanutlin with MDM2 is not very strong, caution~~*Caution* should be used when interpreting any mouse toxicology data. It is important to note that none of the mice changed more than 20% of 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* and idasanutlin combination therapy in clinical studies.

Figure 4: DoHH-2 DLBCL Xenograft Model: Tumor Volume Analysis

The figure has been updated.

SECTION 1.3.2: Quality Development

As of ~~10 June 2015, the SDP formulation has been tested in 24 patients with acute myeloid leukemia (AML) and 41 patients with solid tumors and NHL. In all, 56~~*13*

September 2016, 357 patients have been treated with ~~the new SDP formulation and 265 patients with~~ idasanutlin (both formulations): ~~105~~*191* patients with acute myeloid leukemia (AML) and ~~160~~ *166* patients with solid tumors ~~and~~*or* NHL.

SECTION 1.3.3: Clinical Studies with RO5045337 and Idasanutlin

~~To date, idasanutlin has~~*As of 13 September 2016, idasanutlin had* been studied in ~~265~~ *298* patients in the Phase I/Ib program, including ~~105~~*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.

~~Evaluable hematologic malignancy response assessments are available for 29~~*In the Phase I/Ib AML study, NP28679, 46* patients ~~with AML~~*were* treated with ~~idasanutlin~~ monotherapy ~~in Study NP28679 (Part 1 "plus extension"), 23~~*and 76* patients *were* treated with ~~idasanutlin in~~ combination *therapy* with cytarabine ~~(Part 2), and 38 patients treated with idasanutlin in the presence (21 patients) or absence (17 patients) of cytarabine (Part 2 extension) as of the clinical cutoff date 25 February 2015~~.

As of the clinical cutoff date (~~25 February 2015~~*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:

[•]

Eight of 9 patients were evaluable for response in the Part 1 extension. Response assessments indicated ~~2 patients with~~*2 patients each with CR or complete remission with incomplete platelet count recovery (CRp) or* CRi/MLFS (1 patient bridged to an allogeneic transplant and 1 ~~patient remains in the study >1 year following initiation)~~ *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 patient with CRi/MLFS, and 2* patients ~~with idasanutlin monotherapy and 1 patient who~~ *each with a PR and HI.*

[•]

In Part 4 of the study, ~~4 of 14~~ *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 ~~25 February 2015~~*, 15 April 2016*; enrollment ~~ongoing and completion expected mid July 2015~~*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.

Table 1: Completed, Ongoing, and Planned Idasanutlin Studies

The table has been updated.

SECTION 1.3.3.1: Clinical Pharmacology Summary

Only one ~~inactive~~ 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 impact on idasanutlin maximum concentration values (C_{max}) but increased AUC values by 32%, which suggests a minimal (no clinically significant) drug-drug interaction (DDI) potential with a single use of a strong/moderate CYP3A4 or CYP2C8 inhibitor *(assuming the same minimal effect, as the two isozymes have the metabolic pathway for idasanutlin)*. However, a concomitant second strong/moderate inhibitor of the other CYP pathway (e.g., adding CYP2C8 *inhibition* to CYP3A4 *inhibition*) may increase idasanutlin exposure to a clinically significant level. Because some NHL patients receive strong/moderate CYP3A4 inhibitors for prophylactic or treatment purpose, in this protocol CYP2C8 inhibitors will be prohibited to prevent double-blockade DDI. UGT1A3 may be a major clearing enzyme *for idasanutlin*; its strong inhibitor gemfibrozil is also a CYP2C8 inhibitor that will be excluded from the current study.

As idasanutlin is a substrate for both CYP3A4 and CYP2C8, the known inducers of CYP3A4 and CYP2C8 will also be prohibited from the current study to prevent loss of exposure for idasanutlin.

There is no relevant DDI expected between the two combined drugs *(neither between rituximab and idasanutlin nor between obinutuzumab and idasanutlin)* in the present study. No correlation was apparent between idasanutlin plasma concentration and QTcF.

SECTION 1.3.3.2: Clinical Safety of Idasanutlin
Solid Tumors (Studies NP27872 and NP28902)

~~In Study NP28902, all patients in Part 1, Part 2, and Part 3 experienced at least one adverse event and the majority of patients (85%) who continued in the optional extension part experienced adverse events during this phase of the study. The five most common adverse events reported by the patients in Parts 1, 2, and 3 included diarrhea, nausea, vomiting, fatigue, and constipation; whereas, patients who continued in the~~

~~extension part experienced nausea, diarrhea, platelet count decrease, vomiting, and decreased appetite as the most common adverse events. Gastrointestinal events were the most common related adverse events across all these treatment groups and only occurred during the days of treatment. These were reversible and manageable with anti-emetics and anti-diarrheals for subsequent cycles.~~

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 anti-diarrheal treatments for subsequent cycles.

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 ~~25 February 2015~~*15 April 2016*, all patients *in NP28679* (n~~=105~~)*=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 ~~63 of 105~~ *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 ~~these events, 20~~ *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 ~~25~~*27* deaths reported during the study, of which ~~15~~*16* deaths were associated with or resulted from adverse events. Of the ~~6~~ *8* deaths considered by investigators to be related to study treatment, the causes of death were identified as sepsis (~~2~~*3* patients), pneumonia (1 patient), *Clostridium difficile* infection (1 patient), *Scedosporium* infection (1 *patient), neutropenic colitis (1* patient), and neutropenic sepsis (1 patient).

[•]

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 ~~formulation (Parts 1 and 2, Parts 1 and 2 extension [enrollment ongoing~~; 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)

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. 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.

SECTION 1.4: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

~~In studies of obinutuzumab monotherapy in patients with relapsed or refractory NHL, although the proportion of patients who had a response (either CR or PR) at the end of treatment ranged from 28% to 58%, the CR rate only ranged from 0% to 19%, indicating~~ *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 (Section 1.2.2.1).

[•]

However, based on the fact that the majority of B-lymphoid malignancies, including NHL and CLL, express wild-type p53 and the complementary mechanisms of action involving increased apoptosis (MDM2 antagonists) or direct cell death (obinutuzumab *or rituximab*), the combination of ~~both compounds~~*MDM2 antagonists and obinutuzumab or rituximab* has the potential for superior efficacy *compared to single-agent treatment* in treating B-lymphoid malignancies. The different mechanisms of action (anti-CD20) and two different "late-merging" apoptosis pathways further reduce likelihood of (early) resistance.

In vivo, the combination of obinutuzumab *or rituximab* with the MDM2 inhibitor idasanutlin resulted in robust combined anti-tumor efficacy in p53 wild-type xenograft models (Z-138 and DoHH). These preclinical data strongly support the investigation of obinutuzumab *or rituximab* and idasanutlin as combination therapy in clinical studies for CLL and follicular NHL and DLBCL (Herting et al. 2014; Herting et al. 2016).

Although there is potential of overlapping toxicity with regard to bone marrow suppression *(*anemia, neutropenia, and thrombocytopenia*;* see Table 14) between obinutuzumab *or rituximab* and idasanutlin, the Grade • 3 adverse event rates of hematological 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 a potential delay plan are in place, despite the low starting dose for idasanutlin.

~~During the escalation part, approximately 9• 40 patients will be enrolled in dosing groups of 3• 6 patients each and the dose for idasanutlin will be escalated between dosing groups.~~

In summary, Study BH29812 has been designed to explore different doses of idasanutlin in combination with a fixed dose of obinutuzumab *or rituximab* in patients with R/R FL and DLBCL*, respectively*, with the primary objective to determine the MTD in combination with obinutuzumab *for R/R FL and the MTD in combination with rituximab for R/R DLBCL* and the response rates in addition to safety, pharmacokinetics, and exploratory PD parameters in Phase II. 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.

With the below mentioned risk-minimization measures in place (see Section 5.1), the benefit• risk is considered acceptable for the use of idasanutlin in combination with obinutuzumab *or rituximab* in this Phase Ib/II study (see Table 17 ,Table 18, Table 19, and Table 20).

SECTION 2: OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of obinutuzumab in combination with idasanutlin in patients with ~~relapsed or refractory FL or DLBCL.~~*R/R FL and rituximab in combination with idasanutlin in patients with R/R DLBCL.* Specific objectives and corresponding endpoints for the study are outlined below.

In this study, "study treatment" refers to the ~~combination of~~*protocol-mandated treatments under study (i.e.,* obinutuzumab~~ with~~*,* idasanutlin~~ during induction treatment~~*,* and ~~to obinutuzumab during maintenance treatment in FL.~~*rituximab).*

SECTION 2.1: SAFETY OBJECTIVES AND ENDPOINTS

The safety objectives for this study are as follows:

- To determine the recommended Phase II dose (RP2D) for idasanutlin when given in combination with a fixed dose of obinutuzumab *or rituximab* on the basis of the incidence of DLTs during the *DLT windows (see Section 3.1.2.1)* of study treatment
- To evaluate the safety and tolerability of obinutuzumab *or rituximab* in combination with idasanutlin, including DLTs, on the basis of the following endpoints:

  Nature, frequency, severity, and timing of adverse events

  Changes in vital signs, electrocardiograms (ECGs), and clinical laboratory results during and following study treatment administration

SECTION 2.2: EFFICACY OBJECTIVES

The objective will be assessment of response 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 5), hereinafter referred to as *modified* Lugano 2014 criteria. Response will be determined by an Independent Review Committee (IRC) and by the investigator.

SECTION 2.2.1: Primary Efficacy Objective and Endpoint

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

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

SECTION 2.2.2: Secondary Efficacy Objectives and Endpoints

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

[•]

SECTION 2.2.3: Exploratory Efficacy Objective and Endpoints

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of obinutuzumab in combination with idasanutlin *in R/R FL and rituximab in combination with idasanutlin in R/R DLBCL* on the basis of the following endpoints:

- For patients ~~with FL~~ 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 (expansion only)

[•]

SECTION 2.3: PHARMACOKINETIC OBJECTIVES AND ENDPOINTS

The PK objectives for this study are as follows:

- To characterize the PK profiles of obinutuzumab *or rituximab* and of idasanutlin and its metabolites (if appropriate) to support dose escalation
- To assess potential PK interactions between idasanutlin and obinutuzumab *or rituximab*
- To explore exposure• effect (including PD, efficacy, and adverse event) relationships

SECTION 2.4: BIOMARKER OBJECTIVES AND ENDPOINTS

[•]

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

  Non-inherited biomarkers from tumor tissue samples and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL *(see* Table 13*)*

  Non-inherited biomarkers *from serum and whole blood*:

[•]

SECTION 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 idasanutlin in combination with obinutuzumab in patients with R/R FL ~~or~~ *and rituximab in combination with idasanutlin in 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 RP2D for idasanutlin *in combination with obinutuzumab for FL and in combination with rituximab for DLBCL. Dose escalation starts with idasanutlin* in combination *with obinutuzumab in all patients (FL and DLBCL) until the MTD (Regimen A)* (see Section 3.1.2) followed by*:* ~~an expansion phase in which idasanutlin will be given at the RP2D. All patients will receive induction treatment with obinutuzumab and~~

- *Dose confirmation and potential dose escalation in DLBCL patients for idasanutlin in combination with rituximab to determine the RP2D for this combination.*

- *Dose confirmation and potential dose escalation in FL patients for a different regimen (Regimen B, obinutuzumab given alone in Cycle 1 followed by idasanutlin and obinutuzumab in combination from Cycles 2 to 6) to determine the RP2D for this regimen.*

RP2D(s) and regimens for FL and DLBCL will be decided at the end of dose-escalation phase, and two different RP2Ds and/or regimens may apply for FL and DLBCL, respectively.

In the expansion phase, patients with FL will receive idasanutlin at the RP2D of the selected regimen (A or B) in combination with obinutuzumab, and patients with DLBCL will receive idasanutlin at the RP2D in combination with rituximab.

Patients with R/R FL enrolled in the dose-escalation phase may be eligible to receive post-induction treatment (referred to as maintenance) with obinutuzumab (see Section 3.1.2.2 and Section 3.1.3 for details on treatment regimens).

Patients with R/R FL enrolled in the expansion phase may be eligible to receive maintenance treatment with obinutuzumab 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 expansion phase may be eligible to receive post-induction treatment (referred to as consolidation) with rituximab and idasanutlin (see Section 3.1.3 for details on treatment regimens).

A study schema is provided in Figure 6. Refer to Sections 3.1.2 and 3.1.3 for details on the treatment regimens.

Figure 6: Study Schema

The figure has been replaced to reflect the updated study design.

SECTION 3.1.2: Dose-Escalation Phase (Part 1)

The purpose of the dose-escalation phase (Part 1) is to identify the RP2D *and regimen* for idasanutlin when combined with a fixed dose of 1000 mg of obinutuzumab in patients with R/R FL and *the RP2D for idasanutlin when combined with 375 mg/m² of rituximab in patients with R/R* DLBCL. The RP2D will be based on MTD of idasanutlin when combined with a fixed dose of obinutuzumab *or with 375 mg/m² of rituximab,* but will also include all safety data during treatment. *There could be two different RP2Ds and/or regimens dependent on the combinations of idasanutlin plus obinutuzumab or idasanutlin plus rituximab.*

During the escalation phase, approximately 9• 40 patients will be enrolled in dosing groups of 3• 6 patients each and will be treated at escalating doses of idasanutlin in accordance with the treatment regimen and dose-escalation rules described in Section 3.1.2.2.

Patients will be closely monitored for adverse events during a DLT assessment window, defined as the first treatment cycle *for Regimen A and the first two treatment cycles (one cycle of idasanutlin combination treatment) for patients enrolled in bridging cohort(s) in which idasanutlin will start at Cycle 2 (Regimen B). See Section 3.1.2.2 for treatment regimens.* Adverse events meeting the criteria for DLT, as defined below (see Section 3.1.2.1), will be reported to the Sponsor within 24 hours (see Section 5.4.2).

Patients experiencing a DLT during the ~~first cycle~~ *DLT window* 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 who has not been previously treated in the study. Patients who miss one or more doses of obinutuzumab*, rituximab,* or idasanutlin during the DLT assessment window for reasons other than a DLT will also be replaced. ~~Patients with FL who achieve CR, PR, or SD during induction will also receive maintenance treatment with obinutuzumab.~~

SECTION 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 cycle *(or the first two cycles in the bridging cohorts for patients with FL who start idasanutlin at C*ycle 2*)* of treatment and assessed by the investigator as not clearly related to the patient's underlying disease:

- *Any Grade 5 adverse event unless unequivocally due to the underlying malignancy or extraneous causes*

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- *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 (according to Hy's Law) and will be considered a DLT*
- 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 >5 days) or a documented infection

  Grade 4 neutropenia lasting >7 days

  Grade 3 or 4 thrombocytopenia *if associated with Grade ≥ 3 bleeding* ~~that results in significant bleeding per the investigator's judgment~~

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SECTION 3.1.2.2: Treatment Regimens

Induction treatments will be administered in 28-day cycles, as outlined in Table 2. Intrapatient dose escalation is not permitted in this study. The starting dose for idasanutlin will be 100 mg QD. The dose for idasanutlin will be increased by at least 50 mg from the preceding dose level. *During the dose-escalation phase, patients will be enrolled according to the schema in Figure 6. 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 defined DLT window before enrollment commences in the next cohort.*

Patients in the first cohort will begin with a starting oral dose of 100 mg of idasanutlin QD on Days 1•5 of each cycle in combination with a flat dose of obinutuzumab 1000 mg intravenous (IV) on Days 1, 8, and 15 of Cycle 1 and Day 1 of Cycles 2•6 (see Table 2 and Figure 11 for details on treatment regimens). This regimen is referred to as Regimen A.

Following the identification of the MTD for idasanutlin in combination with obinutuzumab, a bridging cohort of DLBCL patients will be opened to test this MTD in

combination with rituximab (375 mg/m^2 on Day 1 of each cycle; see Figure 6, Figure 12, and Table 2).

If safety and tolerability allow, idasanutlin dose escalation may be explored in combination with rituximab in patients with DLBCL until identification of a new MTD (see Figure 6). A different RP2D in combination with rituximab maybe chosen based on a different MTD.

Following the identification of the MTD for idasanutlin in combination with obinutuzumab, a bridging cohort of FL patients will be opened to test this MTD in a different regimen, referred to as Regimen B. Obinutuzumab will be given alone in Cycle 1 and in combination with idasanutlin in Cycles 2•6 (see Figure 6, Figure 12, and Table 2).

If safety and tolerability allow, idasanutlin dose escalation may be explored with this Regimen B in patients with FL until identification of a new MTD (see Figure 6). The RP2D and regimen for patients with FL will be decided at the end of the dose-escalation phase. Two different RP2Ds and/or regimens may apply for FL and DLBCL, respectively.

After the last patient in each cohort has completed the DLT observation period, the Sponsor, in consultation with the investigators, will evaluate the next dose recommended according to the modified continual reassessment method with overdose control (mCRM; see Section 3.1.2.3) and agree on doses for the subsequent cohort, 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, de-escalated, or an additional cohort at the same dose level may be enrolled.

During the dose-escalation phase, study treatment will be administered as outlined in Table 2. Patients with FL who achieve a CR or PR at the EOI will also receive maintenance treatment with obinutuzumab. 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 (see Table 3).

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.

Table 2: Induction Treatment for Dose-Escalation Phase

The table has been updated to reflect the change in regimen.

Table 3: Maintenance Treatment during the Dose-Escalation Phase for Patients with Follicular Lymphoma

The table has been added to reflect the change in regimen.

SECTION 3.1.2.3: Dose-Toxicity Model with mCRM

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The first patient in each cohort will be observed for safety for 1 week *after Cycle 1, Day 1* before enrolling additional patients in the cohort. After the last patient in each cohort has completed the 1-cycle DLT observation period, the Sponsor and investigators will evaluate the next dose recommended by the mCRM design and agree on the dose for the subsequent cohort. At each dose-escalation step, the dose can be escalated, de-escalated, or an additional cohort at the same dose-level can be enrolled.

The starting dose for idasanutlin will be 100 mg and the fixed dose for obinutuzumab will be 1000 mg. *The dose for rituximab starting from the bridging cohort for DLBCL patients will be 375 mg/m^2.*

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

SECTION 3.1.3: <u>Expansion Phase (Part 2)</u>

The expansion phase is designed to further assess the safety and efficacy of obinutuzumab in combination with idasanutlin at the RP2D *with the selected regimen in patients with R/R FL and of rituximab in combination with idasanutlin at the RP2D in patients with R/R DLBCL.* Approximately 80 patients (40 patients with R/R FL and 40 patients with R/R DLBCL) will be enrolled during the expansion phase and treated as described below. *The start of the expansion phase may not happen simultaneously for the two indications.*

All patients will receive 6 cycles of induction treatment, administered in 28-day cycles, as outlined in Table 6. Patients with FL who achieve a CR *or* PR~~, or SD~~ at the EOI will receive maintenance treatment with obinutuzumab ~~1000 mg IV every 2~~ *and idasanutlin. Patients with DLBCL who achieve a CR or PR at the EOI will receive consolidation treatment with rituximab 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 7).*

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.

Table 6: Induction Treatment for the Expansion Phase

The table has been updated to reflect the change in regimen.

Table 7: Post-Induction Treatment for the Expansion Phase

The table has been added to reflect the change in regimen.

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

SECTION 3.3.1: Rationale for Treatment Combination

Obinutuzumab ~~has~~ *and rituximab have* been shown to be safe and active as monotherapy in patients with R/R NHL (Section 1.2.2).

Based on the fact that the majority of B-lymphoid malignancies, including NHL and CLL, bear wild-type p53, and the complementary mechanisms of action involving increased apoptosis (MDM2 antagonists) or direct cell death (obinutuzumab *and rituximab*), the combination of ~~both compounds~~*an anti-CD20 antibody (obinutuzumab or rituximab) and a MDM2 antagonist* has the potential for superior efficacy *compared to single-agent treatment* in treating B-lymphoid malignancies. The combination of obinutuzumab *or rituximab* with the MDM2-antagonist idasanutlin resulted in enhanced cell death of p53 wild-type NHL tumor cells. Therefore, the complementary mechanism of actions of these drugs promises additive effect and, there are first attempts to quantify cooperative effects in system biology based PD model. In fact, combinatorial efficacy of different pro-apoptotic drugs in NHL can be described in a quantitative way by a signaling model of CD20 pharmacodynamics (Harrold et al. 2012).

A xenograft model of MCL shows more durable response only in idasanutlin in combination with the anti-CD20 drug obinutuzumab (see Section 1.3.1, Figure 2). The addition of obinutuzumab or rituximab to idasanutlin may primarily prevent relapse. Enhanced tumor control in the Z-138 MCL and a high bar DLBCL xenograft model was observed with an obinutuzumab *or rituximab* plus idasanutlin combination over idasanutlin monotherapy *or an anti-CD20 antibody alone* (see Section 1.3.1). These

data support further evaluation of the combination of idasanutlin and obinutuzumab *or rituximab* in clinical studies in lymphoma.

SECTION 3.3.2: Rationale for Idasanutlin Starting Dose

Therefore, a daily dose of 100 mg of the idasanutlin SDP formulation, which is roughly the equivalent of 200 mg idasanutlin MBP formulation, seems to be a safe starting dose with potential to activate p53 as determined by the MIC-1 PD Marker in combination with obinutuzumab *or rituximab*.

SECTION 3.3.3: Rationale for Dosing Regimen

The study will start with obinutuzumab standard dosing in combination with idasanutlin from Cycles 1 to 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 from Cycles 2 to 6 will be explored (bridging cohorts) 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 on Day 1 in subsequent cycles. Those 3 doses of obinutuzumab, when combined with idasanutlin at higher doses in the same treatment cycle, may induce more profound hematologic toxicities. Staggered idasanutlin 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.

The dose of rituximab of 375mg/m^2 is the recommended dose in the NHL population and is the standard of care. For DLBCL patients 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). The dose and schedule in the consolidation phase will be 375 mg/m^2 every 2 months in combination with idasanutlin to explore potential benefit with consolidation treatment. 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.

SECTION 3.3.4: Rationale for Pharmacokinetic Assessments

The PK data are important to meet at least three major objectives: to support dose escalation, to assess potential PK interactions between idasanutlin and obinutuzumab *or rituximab*, and to explore exposure-effect (including PD, efficacy, and adverse events) relationships. The data from the current study may be combined for further analysis (e.g., popPK) with those generated from other studies.

SECTION 4.1.2: Exclusion Criteria

- *Treatment with the following agents within 7 days prior to the first dose of idasanutlin:*

  CYP2C8 inhibitors including gemfibrozil (also a UGT1A3 inhibitor)

CYP2C8 substrates

OATP1B1/3 substrates

- *Treatment with the following agents within 14 days prior to the first dose of idasanutlin:*

  Strong CYP3A inducers including rifampin (also a CYP2C8 inducer)

- *Chronic use of CYP2C8 or OATP1B1/3 substrates*
- Known hypersensitivity or allergy to murine products or any component of the obinutuzumab*, rituximab,* or idasanutlin formulations
- Active bacterial, viral, fungal, or other infection

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

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a Phase Ib/II, open-label, multicenter, non-randomized study of obinutuzumab in combination with idasanutlin in patients with *R/R FL and obinutuzumab or rituximab in combination with idasanutlin in patients with R/R* DLBCL. During the dose-escalation phase, patients with R/R FL or DLBCL will be assigned to dosing groups through an interactive voice or Web-based response system (IxRS). *Following determination of the MTD of idasanutlin in combination with obinutuzumab, bridging cohort(s) of DLBCL patients will be opened to confirm the MTD of idasanutlin in combination with rituximab. Following determination of the MTD of idasanutlin in combination with obinutuzumab, bridging cohort(s) of FL patients will be opened to explore a different regimen (Regimen B, obinutuzumab alone at Cycle 1 and obinutuzumab in combination with idasanutlin at Cycles 2 to 6).* During the expansion phase, patients with ~~relapsed or refractory FL or DLBCL~~ *R/R FL* will be treated at the RP2D of idasanutlin plus 1000 mg obinutuzumab *with the selected regimen, and patients with R/R DLBCL will be treated at the RP2D of idasanutlin plus 375 mg/m^2 rituximab.*

SECTION 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.

Figure 10: Guidelines for Obinutuzumab Infusions: Second and Subsequent Infusions

The figure has been updated.

SECTION 4.3.2.3: 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 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 • 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 4.3.2.6) and at the first infusion rate (see Table 8).

Rituximab infusions will be administered according to the instructions in Table 8.

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

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

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.

No dose modification for rituximab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.5.

Premedication with a corticosteroid, analgesic/antipyretic, and antihistamine, as outlined in Section 4.3.2.6, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 9.

Table 8: Administration of First and Subsequent Infusions of Rituximab

The table has been added.

SECTION 4.3.2.4: Induction Treatment with Obinutuzumab or Rituximab and Idasanutlin

Patients will receive 6 cycles of induction treatment consisting of obinutuzumab or rituximab and idasanutlin as outlined in Table 6. For patients with FL enrolled in the bridging cohort(s), obinutuzumab will be given alone at Cycle 1, and the obinutuzumab and idasanutlin combination will be given from Cycles 2 to 6.

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

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

Please refer to Section 3 for further details.

Figure 11: Treatment with Idasanutlin and Obinutuzumab: Schedule of Treatment

The figure has been added.

Figure 12: Escalation Phase (DLBCL Bridging Cohort[s]) and Expansion Phase with Idasanutlin and Rituximab: Schedule of Treatment

The figure has been added.

Table 9: Premedication

The table has been updated to reflect the change in regimen.

SECTION 4.3.3: Investigational Medicinal Product Accountability

All IMPs required for completion of this study (obinutuzumab*, rituximab,* and idasanutlin) will be provided by the Sponsor.

SECTION 4.3.4: Post-Study Access to Obinutuzumab, *Rituximab*, and Idasanutlin

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

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

SECTION 4.4: CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from ~~7~~*14* days prior to the screening period to the visit at EOI or at the end of Maintenance *or consolidation* treatment, whichever occurs later.

SECTION 4.4.2: Prohibited Therapy

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- Vaccination with live vaccines is not recommended during treatment with obinutuzumab *or rituximab* and until B-cell recovery.

Idasanutlin is metabolized mainly by 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), it is not a sensitive CYP3A or CYP2C8 substrate as summarized in Section 1.3.3.1 and thus its metabolism* ~~, which~~ may *only* be affected by concomitant CYP3A *and* CYP2C8~~, and UGT inhibitors and~~ inducers *or dual CYP3A and CYP2C8 inhibition.* Idasanutlin inhibits CYP2C8 metabolism, which may affect concomitant ~~OATP1B1/3~~ *CYP2C8* substrates, and its M4 metabolite is an organic anion-transporting polypeptide (OATP)-1B1/3 transporter inhibitor that may affect concomitant *OATP1B1/3* ~~CYP2C8~~ substrates. Thus, *in order to prevent undesirable drug-drug interactions,* the use of any *medication listed in Table 10 (CYP2C8 substrates and inhibitors), Table 11 (strong CYP3A inducers), and Table 12 (OATP1B1/3 substrates) are either prohibited during the study within the DLT evaluation window in the escalation phase or allowed after the DLT evaluation window, after washing out in sufficient duration (for inhibitors) or concomitant use with caution (for inducers)in order to prevent undesirable drug-drug interactions.* Note that gemfibrozil is also a UGT1A3 inhibitor that will be excluded from this study and that CYP3A4 inhibitors are not excluded. ~~(preliminary data suggest minimal [not clinically significant] drug–drug interaction potential with posaconazole, a strong CYP inhibitor)~~.

Table 10: Prohibited CYP2C8 Substrates, Inhibitors, *and Inducers*

The table has been updated.

Table 11: Prohibited *Strong* CYP3A4 Inducers

The table has been updated.

Table 12: Prohibited OATP1B1/3 Substrates

The table has been updated.

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

SECTION 4.5.1: Informed Consent Forms and Screening Log

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 time 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.*

SECTION 4.5.6.1: Local Laboratory Assessments

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

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- *Bone marrow assessment*

SECTION 4.5.6.2: Central Laboratory Assessments

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

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- *Serum samples for rituximab PK analysis using a validated assay*

SECTION 4.5.7: Electrocardiograms

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

SECTION 4.5.8.3: Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to obinutuzumab*, rituximab,* and idasanutlin, FL, DLBCL, or other types of cancer:

[•]

SECTION 4.6.2: Study Treatment Discontinuation

Study treatment (obinutuzumab *or rituximab* and idasanutlin) should be permanently discontinued in patients who experience any of the following:

- DLT during ~~Cycle 1~~*the DLT window* in patients enrolled in the dose-escalation phase

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SECTION 5.1: SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with obinutuzumab*, rituximab,* and idasanutlin in completed and ongoing studies. The anticipated important safety risks of obinutuzumab*, rituximab, and idasanutlin* are outlined below. Refer to the Obinutuzumab*, Rituximab,* and Idasanutlin Investigator's Brochures for a complete summary of safety information and prescribing information.

SECTION 5.1.1: Risks Associated with Obinutuzumab

As of ~~the safety PBRER cutoff of 30 April 2015~~*4 July 2016,* the following adverse events are considered to be important risks associated with obinutuzumab: IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia), infections (including PML and HBV reactivation), prolonged B-cell depletion, impaired immunization response worsening of preexisting cardiac conditions, gastrointestinal perforation*, immunogenicity, and second malignancies. These events, with the exception of prolonged B-cell depletion, immunogenicity, and second malignancies, are described below.*

SECTION 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.

SECTION 5.1.2.1: Infusion-Related Reactions

Acute IRRs are very common in patients receiving rituximab (occurring in • 10% of patients) based on clinical trial experience. However, serious IRRs are uncommonly reported (occurring in • 1 of 1,000 and < 1 of 100 patients) and are rarely fatal (occurring in • 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.

SECTION 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.

SECTION 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.

SECTION 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.

SECTION 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.

SECTION 5.1.2.6: Tumor Lysis Syndrome

Patients treated with rituximab may be at risk for TLS. Severe 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.

SECTION 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.

SECTION 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.

SECTION 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.

SECTION 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 ~~as of the clinical cutoff date of 05 May 2015 for Study~~ 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.*

All 99 patients in Study NP27872*Many of the toxicities* experienced at least one adverse event, with *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, decreased appetite, and *), 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.

SECTION 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 events. Grade 3• 5 adverse events were frequently*event observed across treatment groups and indications. It has been* reported in *a large majority of* patients (63.6%) with solid tumors 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.*

SECTION 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 5.1.5). 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.

SECTION 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 Clostridium difficile infection should be investigated.

SECTION 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 5.1.5.

SECTION 5.1.3.5: Electrolyte Disorders

Electrolyte disorders (hypercalcemia, hyperkalemia, hypernatremia, hypocalcaemia, hypokalemia, hypomagnesemia, hyponatremia, hyperphosphatemia, and hypophosphatemia) 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.

SECTION 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.~~reported by the patients in Parts 1, 2, and 3 included diarrhea, nausea, vomiting, fatigue, and constipation; whereas, patients who continued in the extension part experienced nausea, diarrhea, platelet count decreased, vomiting, and decreased appetite as the most common adverse events. Gastrointestinal events were the most common related adverse events across all these treatment groups~~

~~Serious adverse events were reported in 32 of 99 patients in Study NP27872, most commonly thrombocytopenia, febrile neutropenia, neutropenia, anemia, and leukopenia. The most frequently reported serious adverse events in Study NP28902 in 16 of 61 patients were pyrexia, cellulitis, and dehydration. Overall, 7 deaths in Study NP27872 and 3 deaths in Study NP28902 were reported. Of the 7 deaths reported in Study NP27872, 5 were attributed to disease progression, one was due to intra-abdominal hemorrhage with pulmonary embolism (unrelated), and one was due to pulmonary embolism (remotely related). In Study NP28902, the cause of death for 2 patients was attributed to disease progression. The cause of death for the other patient in Study NP28902 was fatal adverse event pneumonia aspiration, considered unrelated to study drug.~~

~~In the AML setting, as of the clinical cutoff date (25 February 2015), all 105 patients enrolled in Study NP28679 experienced at least one adverse event. The most common adverse events across all study groups were of the SOC gastrointestinal disorders, in particular diarrhea and nausea. Serious adverse events were reported in 63 of 105 patients across the study, most commonly infectious events and blood and lymphatic system disorders. Overall, there were 25 deaths reported during the study, 9 of which were attributed to progressive disease and 15 of which were associated with or due to serious adverse events. Of the 6 fatal serious adverse events considered by investigators to be related to study treatment, the causes of death were identified as sepsis in 2 patients and pneumonia, *Clostridium difficile* infection, scedosporium infection, and neutropenic sepsis in 1 patient each.~~

SECTION 5.1.4: Risk of Overlapping Toxicities

Overlapping toxicities across *idasanutlin and* obinutuzumab are neutropenia and thrombocytopenia (see Table 14). *Overlapping toxicities across idasanutlin and rituximab are neutropenia and thrombocytopenia (see Table 15).*

Table 15: Overlapping Toxicities: Idasanutlin and Rituximab

The table has been added.

SECTION 5.1.5: Management of Specific Adverse Events

During induction, study treatment may be delayed for toxicity for a maximum of 21 days. If study treatment is delayed for >21 days, obinutuzumab *or rituximab* and idasanutlin treatment will be permanently discontinued (see Table 16, Table 17, and Table 18).

Treatment delays apply to all toxicities described below; dose modifications apply only to toxicities that are considered to be related to idasanutlin. There will be no dose reductions of obinutuzumab *or rituximab.*

[•]

SECTION 5.1.5.1: Toxicities during Induction Treatment

Table 17: Guidelines for Management of Hematologic Toxicities That Occur during Induction Treatment (Except for Days 8 and 15 of Cycle 1)

The table has been updated.

Table 19: Guidelines for Management of Non-Hematologic Toxicities

The table has been updated.

SECTION 5.1.5.2: Toxicities during Maintenance Treatment

Table 20: Guidelines for Management of Toxicities That Occur during Maintenance Treatment

The table has been updated.

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

[•]

- *Grade • 2 Clostridium difficile infection*
- *Second malignancies*

SECTION 5.3.1: Adverse Event Reporting Period

An exception is made for Grade 3 or 4 infections (related and unrelated) *in patients who received obinutuzumab,* which should be reported up to 2 years after the last dose of ~~study treatment~~*obinutuzumab*.

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

SECTION 5.3.5.8: Deaths

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. ~~The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "**sudden death**" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

SECTION 5.3.5.10: Lack of Efficacy or Worsening of Lymphoma

In most cases, the expected pattern of progression will be based on the *modified* Lugano 2014 criteria (see Appendix 5).

SECTION 5.3.5.11: Hospitalization or Prolonged Hospitalization

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:~~The following hospitalization scenarios are not considered to be adverse events:~~

[•]

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:~~The following hospitalization scenario is not considered to be a serious adverse event, but should be reported as *an* adverse event instead:~~

SECTION 5.3.5.12: Adverse Events Associated with an Overdose or Error in Drug Administration

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/m²). No additional safety signals were identified.

SECTION 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 ~~3~~*18* months after the last dose of study treatment *for those receiving obinutuzumab and idasanutlin and within 12 months after the last dose of study treatment for those receiving rituximab and idasanutlin*.

SECTION 5.6: POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as within 90 days after the last dose of study treatment*)*, if the event is believed to be related to prior study treatment. 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~~*obinutuzumab*. *The sponsor should also be notified of events of second malignancies indefinitely (even if the study has been closed) for patients who received obinutuzumab.*

SECTION 5.7: EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

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

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This Phase Ib/II, open-label, multicenter, non-randomized dose-escalation study will evaluate the safety, efficacy, and pharmacokinetics of idasanutlin and obinutuzumab in patients with R/R FL *and of idasanutlin and rituximab in R/R* DLBCL*.*

SECTION 6.3: SAFETY ANALYSES

The major safety objective is to determine the DLT of idasanutlin in combination with obinutuzumab *or rituximab.*

[•]

The primary safety population will include patients who received at least one dose of *any* component of the combination.

SECTION 6.4: EFFICACY ANALYSES

The primary and secondary efficacy analyses will be performed and will include all patients enrolled in the expansion phase, who received ~~idasanutlin for a~~t least ~~5 days.~~ *one dose of any component of the combination.* Data from patients ~~from selected cohorts of~~ *who were dosed at the RP2D with the recommended Phase 2 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 5).

SECTION 6.4.1: 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 EOI. Patients without a post-baseline tumor assessment will be considered non-responders. ~~The primary efficacy population will include patients who received at least one dose of *any* component of the combination.~~

SECTION 6.4.3: 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*

[•]

SECTION 6.5: PHARMACOKINETIC ANALYSES

Individual and mean serum ~~and plasma~~ concentrations of obinutuzumab *or rituximab* and *plasma concentrations of* idasanutlin ~~versus time data~~ will be tabulated and plotted *after appropriate grouping*.

SECTION 6.7: INTERIM ANALYSES

~~It is anticipated that at least one interim analysis will be conducted during the expansion phase of the study when at least 15 patients per disease indication (FL or DLBCL) have been evaluated for PET-CT defined CR at EOI. *This interim analysis may not happen simultaneously for the two indications if the targeted sample size is reached at considerably different times.*~~

~~During the expansion phase, a predictive probability design (Lee and Liu 2008) may be used to guide early stopping for futility by comparing the observed proportion of patients who achieve a PET-defined CR at EOI in each expansion cohort with historical controls. The earliest interim analysis would occur after at least 15 patients have been evaluated for PET-CT- defined CR at EOI. Data from completed and ongoing studies in similar disease settings will be used as historical controls for comparison.~~

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

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

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 the 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.

SECTION 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.*

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

For more information, refer to the Roche Global Policy on Sharing of Clinical ~~Trials Data~~*Study Information* at the following Website: *http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf*~~http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf~~

APPENDIX 1: Schedule of Activities for Patients with Follicular Lymphoma (Dose-Escalation and Expansion Phases)

The appendix has been updated to reflect changes to the protocol.

APPENDIX 2: Schedule of Activities for Patients with DLBCL

The appendix has been updated to reflect changes to the protocol.

APPENDIX 3: Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab *or Rituximab* and Idasanutlin *in Regimen A*

The appendix has been updated to reflect changes to the protocol.

APPENDIX 4: Schedule of Pharmacokinetic and Pharmacodynamic (MIC 1) Assessments for Obinutuzumab and Idasanutlin in Regimen B

The appendix has been added to reflect changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH IDASANUTLIN IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA** *AND OBINUTUZUMAB OR RITUXIMAB IN COMBINATION WITH IDASANUTLIN IN PATIENTS WITH RELAPSED OR REFRACTORY* **DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	BH29812
VERSION NUMBER:	4
EUDRACT NUMBER:	2015-002100-83
IND NUMBER:	127311
TEST PRODUCT:	Obinutuzumab (RO5072759) *Rituximab (RO0452294)* Idasanutlin (RO5503781)
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 [redacted]

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IB/II STUDY EVALUATING THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN COMBINATION WITH IDASANUTLIN IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA** *AND OBINUTUZUMAB* **OR** *RITUXIMAB IN COMBINATION WITH IDASANUTLIN IN PATIENTS WITH RELAPSED OR REFRACTORY* **DIFFUSE LARGE B-CELL LYMPHOMA**
PROTOCOL NUMBER:	BH29812
VERSION NUMBER:	4
EUDRACT NUMBER:	2015-002100-83
IND NUMBER:	127311
TEST PRODUCT:	Obinutuzumab (RO5072759) *Rituximab (RO0452294)* Idasanutlin (RO5503781)
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

Efficacy Objectives and Endpoints

The objective will be response 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 *modified* Lugano 2014 criteria. Response will be determined by an Independent Review Committee (IRC) and by the investigator.

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

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

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

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

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

Exploratory Objectives and Endpoints

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of obinutuzumab in combination with idasanutlin *in R/R FL and rituximab in combination with idasanutlin in R/R DLBCL* 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 (expansion only)*
- PFS
- EFS
- Disease-free survival (DFS)
- OS
- Additional descriptive analysis based on TP53 status will be performed on the following endpoint:
    - CR at EOI, as determined by the IRC on the basis of PET-CT scans

Safety Objectives

The safety objectives for this study are as follows:

- To determine the recommended Phase II dose (RP2D) for idasanutlin when given in combination with a fixed dose of obinutuzumab *or rituximab* on the basis of the incidence of DLTs during the *DLT windows* of study treatment
- To evaluate the safety and tolerability of obinutuzumab *or rituximab* in combination with idasanutlin, including DLTs, on the basis of the following endpoints:

    Nature, frequency, severity, and timing of adverse events

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

Pharmacokinetic Objectives

The PK objectives for this study are as follows:

- To characterize the PK profiles of obinutuzumab *or rituximab* and of idasanutlin and its metabolites (if appropriate) to support dose escalation
- To assess potential PK interactions between idasanutlin and obinutuzumab *or rituximab*
- To explore exposure• effect (including PD, efficacy, and adverse event) relationships

Biomarker Objectives and Endpoints

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

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

  Non-inherited biomarkers from tumor tissue samples and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL

  Non-inherited biomarkers:

  MIC-1

  Circulating lymphoma cells

  Cell-free circulating tumor DNA

  Lymphocyte immunophenotyping

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 idasanutlin in combination with obinutuzumab in patients with R/R FL *and rituximab in combination with idasanutlin in 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 RP2D and regimen for idasanutlin *in combination with obinutuzumab for FL and in combination with rituximab for DLBCL. Dose escalation starts with idasanutlin* in combination *with obinutuzumab in all patients (FL and DLBCL) until the MTD (Regimen A) followed by:*

- *Dose confirmation and potential dose escalation in DLBCL patients for idasanutlin in combination with rituximab to determine the RP2D for this combination.*

- *Dose confirmation and potential dose escalation in FL patients for a different regimen (Regimen B, obinutuzumab given alone in Cycle 1 followed by idasanutlin and obinutuzumab in combination from Cycles 2 to 6) to determine the RP2D for this regimen.*

RP2D(s) and regimens for FL and DLBCL will be decided at the end of dose-escalation phase, and two different RP2Ds and/or regimens may apply for FL and DLBCL, respectively.

In the expansion phase, patients with FL will receive idasanutlin at the RP2D of the selected regimen (A or B) in combination with obinutuzumab, and patients with DLBCL will receive idasanutlin at the RP2D in combination with rituximab.

Patients with R/R FL enrolled in the dose-escalation phase may be eligible to receive post-induction treatment (referred to as maintenance) with obinutuzumab.

Patients with R/R FL enrolled in the expansion phase may be eligible to receive maintenance treatment with obinutuzumab and idasanutlin.

Patients with R/R DLBCL enrolled in the expansion phase may be eligible to receive post-induction treatment (referred to as consolidation) with rituximab and idasanutlin.

Number of Patients

Overall, approximately 89• 120 patients with R/R FL and DLBCL are expected be enrolled in this study, at approximately 25 investigative sites around the world.

Target Population

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)
- Patients with R/R FL after treatment with at least two prior lines of therapy, including at least one chemoimmunotherapy regimen that contained an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator
- R/R 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 NHL by 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 or magnetic resonance imaging [MRI] scan)
- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL. Further details are provided in the protocol.

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

  If a patient has had anti-lymphoma therapy between the time of the prior biopsy and treatment initiation, a repeat biopsy is highly encouraged.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 18 months after the last dose of study treatment

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

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential (and not using effective contraception), men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$1% per year during the treatment period and for at least 3 months after the last dose of study treatment. Men must refrain from donating sperm for the same period.

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

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

Exclusion Criteria

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

- Known CD20 negative status at relapse/progression.
- Central nervous system lymphoma or leptomeningeal infiltration
- 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 • 2 (according to the NCI CTCAE, v4.0) prior to Day 1 of Cycle 1
- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Treatment with systemic corticosteroids > 20 mg/day prednisone or equivalent

  Patients receiving corticosteroids • 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.
- *Treatment with the following agents within 7 days prior to the first dose of idasanutlin:*

  CYP2C8 inhibitors including gemfibrozil (also a UGT1A3 inhibitor)

  CYP2C8 substrates

  OATP1B1/3 substrates
- *Treatment with the following agents within 14 days prior to the first dose of idasanutlin:*

  Strong CYP3A inducers including rifampin (also a CYP2C8 inducer)
- *Chronic use of CYP2C8 or OATP1B1/3 substrates*
- Clinical conditions requiring treatment with oral or parenteral anticoagulants/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).
- Patients that may refuse blood products and/or have 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,* or idasanutlin formulations
- Active bacterial, viral, fungal, or other infection

  Caution should be exercised when considering the use of obinutuzumab *or rituximab* in patients with a history of recurring or chronic infections.
- Positive for hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at screening
- Known history of HIV positive status

  For patients with unknown HIV status, HIV testing must be performed at screening if not in contradiction with local legislation.
- History of Progressive Multifocal Leukoencephalopathy (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 • 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)
- 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 $< 1.5 \cdot 10^9$/L

  Platelet count $< 75 \cdot 10^9$/L
- Any of the following abnormal laboratory values (unless due to underlying lymphoma):

  Creatinine $> 1.5 \cdot$ the upper limit of normal (ULN) (unless creatinine clearance is normal) or calculated creatinine clearance < 40 mL/min (using the Cockcroft-Gault formula)

  AST or ALT $> 2.5 \cdot$ ULN

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

  INR or PT $> 1.5 \cdot$ ULN in the absence of therapeutic anticoagulation

  PTT or aPTT $> 1.5 \cdot$ ULN in the absence of a lupus anticoagulant
- Pregnant or lactating, or intending to become pregnant during the study

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

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 48 months.

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

Investigational Medicinal Products

Test Product (Investigational Drug)

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/m2 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.

Statistical Methods

Efficacy Analysis

The primary and secondary efficacy analyses will be performed and will include all patients enrolled in the expansion phase, who received at least *one dose of any component of the combination.* Data from patients *who were dosed at the RP2D with the recommended Phase 2 regimen during* the dose-escalation phase may be pooled with the corresponding arm of the expansion phase, depending on their indication.

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 EOI. Patients without a post-baseline tumor assessment will be considered non-responders.

Secondary Efficacy Endpoints

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

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

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 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 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:

- PFS, defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by 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 investigator on the basis of CT scans alone, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first
- 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
- OS, defined as the time from initiation of study treatment to death from any cause

PFS, EFS, DFS, and OS will be summarized descriptively using the Kaplan-Meier method. For the PFS, EFS, and DFS analyses, data for patients without an event of interest will be censored at the date of the last valid tumor assessment, i.e. CR, PR, or SD. For patients without post-baseline tumor assessments, data will be censored at the date of initiation of study treatment plus 1. For the OS analysis, data for patients who have not died will be censored at the date the patient was last known to be alive. Where medians are reached, the corresponding estimated median will be provided, along with the 95% CI using the method of Brookmeyer and Crowley. In addition, where available at the time of the analysis, landmark estimates of the proportion of patients who are event free at 6 months, 9 months, 1 year, and 2 years will be provided, along with 95% asymptotic CIs using Greenwood's formula for standard errors.

Pharmacokinetic Analyses

Individual and mean serum concentrations of obinutuzumab *or rituximab* and *plasma concentrations of* idasanutlin will be tabulated and plotted *after appropriate grouping*. Summary statistics of concentration data will be computed for each scheduled sampling time for each analyte. Interpatient variability and drug accumulation after multiple doses will be evaluated. Compartmental, non-compartmental, and/or population approaches will be considered as appropriate. Potential drug interactions may be assessed by comparison of pharmacokinetics in the current study with historical data. Potential correlations between PK exposure and demographic and pathophysiological covariates may be explored by population PK analysis. Potential correlations between PK exposure and PD, efficacy, and safety endpoints may be explored by graphical analysis and PK-PD modeling. The assessment of PK parameters and related analyses will be performed per the Sponsor's discretion, taking into consideration the appropriateness of the PK data collected and the study outcome.

Biomarker Analysis

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.

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 the 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.

Determination of Sample Size

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 algorithm, as outlined in the protocol. It is anticipated that enrollment of up to eight cohorts of 3• 6 patients each, for a total of 9• 40 patients, will be required to establish the RP2D during the dose-escalation phase (See protocol for modeling details). The estimated probability to require more than 30 patients in the investigated scenarios in the protocol is generally less than 5%

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 (GAUDI study/BO21000) and (Gadolin/GO01297), and 40% in DLBCL assuming an observed PET-defined CR rate of 55%. The protocol provides 90% Clopper-Pearson exact CIs for the probability of achieving an EOI PET-defined CR for a range of observed proportions based on a sample of 40 patients.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
18F-FDG	18F-fluorodeoxyglucose
ABC	activated B cell–like (subgroup)
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AML	acute myeloid leukemia
ASCO	American Society of Clinical Oncology
AUC	area under the concentration• time curve
BID	twice daily
BSA	*body surface area*
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone
CI	*confidence interval*
CLL	chronic lymphocytic leukemia
C_{max}	maximum serum concentration
CR	complete response
CRi	*complete remission with* incomplete blood count recovery
CRp	*complete remission with incomplete platelet count recovery*
CT	computed tomography
CVP	cyclophosphamide, vincristine, and prednisone
CYP	cytochrome
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DFS	disease-free survival
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
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

Abbreviation	Definition
FDA	U.S. Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
G	obinutuzumab (GA101)
GB	obinutuzumab plus bendamustine
GCB	germinal-center B cell–like (subgroup)
G-CHOP	*obinutuzumab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone*
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
HBcAb	hepatitis B core 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
IgH	immunoglobulin heavy
IHC	immunohistochemistry
IMC	internal monitoring committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
iNHL	indolent non-Hodgkin's lymphoma
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous
IxRS	interactive voice or Web-based response system
JC	John Cunningham
LMWH	low-molecular-weight heparin
LPLV	last patient, last visit

Abbreviation	Definition
MBP	microprecipitated bulk powder
mCRM	modified-Continual Reassessment Method with Overdose Control
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
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NK	natural killer
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PR	partial response
QD	once daily
QW	once weekly
R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone
RCR	Roche Clinical Repository
R-DHAP	rituximab plus dexamethasone, cytosine arabinoside, and cisplatin
R-ICE	rituximab plus ifosfamide, carboplatin, and etoposide
RP2D	recommended Phase II dose
R/R	*relapsed or refractory*
SCT	stem-cell transplantation
SD	stable disease
SDP	spray-dried powder
SOC	System Organ Class
$t_{1/2}$	half-life
TGI	tumor growth inhibition
TLS	tumor lysis syndrome
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON NON-HODGKIN'S LYMPHOMA

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

1.1.1 Follicular Lymphoma

Indolent NHLs (iNHLs) are a heterogeneous group of malignant lymphomas and account for approximately one-third of all NHLs. Follicular lymphoma (FL) is the most common subtype of iNHL, accounting for approximately 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 *B-cell Lymphoma 2* (*BCL2)* with the immunoglobulin heavy (IgH) locus and results in deregulated expression of 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 (Zelenetz et al. 2014; Dreyling 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 immunochemotherapy as first-line treatment, most patients will eventually 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 and aggressive NHL, accounting for approximately 30% of all NHLs diagnosed annually (Armitage and Weisenburger 1998). The use of immunochemotherapy, most commonly rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone or prednisone (R-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 of age) with favorable prognostic features, R-CHOP demonstrated a 3-year EFS rate of 79% and a

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

Second-line therapies consist of high-dose chemotherapy regimens, such as R-ICE (rituximab plus ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab plus cisplatin, cytosine arabinoside, and dexamethasone) followed by autologous stem-cell transplantation (SCT). Approximately half of 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 this aggressive therapy.

Specific molecular subsets of DLBCL are associated with an inferior outcome following R-CHOP therapy. Germinal center B cell• like (GCB) DLBCL had a better prognosis than activated (non-germinal) B-cell-like (ABC) DLBCL, with a 3-year survival rate of 84% versus 56%, respectively ($p < 0.001$) (Lenz et al. 2008). Several genetic abnormalities predictive of poor outcome have been identified in DLBCL, including *MYC* rearrangement, *BCL2* and *BCL6* overexpression, and *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 patients with DLBCL, 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 18%• 30% of patients with DLBCL (Lossos and Morgensztern 2006) and are strong predictors of poor overall survival (Young et al. 2008).

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

1.2 BACKGROUND ON OBINUTUZUMAB

Obinutuzumab (also known as GA101) is a novel glycoengineered type II anti-CD20 antibody. Compared with the type I anti-CD20 antibody, rituximab, obinutuzumab is characterized by more potent direct B-cell death induction and increased affinity for Fc•RIII receptors expressed on natural killer (NK) cells, macrophages, and monocytes, resulting in enhanced antibody-dependent *cell-mediated* 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 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, 1.3.1, and 1.4.

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 promising anti-tumor activity of obinutuzumab (Mössner et al. 2010; Dalle et al. 2011) and superiority of obinutuzumab over rituximab (Mössner et al. 2010; Herting et al. 2016).

Further details of the nonclinical studies conducted are presented in the most current 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.

Further clinical details, including results from the CLL cohorts, are presented in 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 relapsed or refractory (R/R) NHL (Studies BO20999, BO21003, and JO21900), the proportion of patients who had a response (complete response [CR] or partial response [PR]) at the end of induction (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 (i.e., CHOP or bendamustine) in patients with previously untreated or R/R NHL (Studies BO21000, and GAO4915g), the proportion of patients with a CR or PR at the end of induction treatment ranged from 82% to 96%. The CR rate was higher with combination therapy (35%• 39%

in previously untreated FL, 39%• 50% in R/R FL, and 55% in previously untreated DLBCL) than with monotherapy.

A Phase III study (GAO4753g) investigated obinutuzumab plus bendamustine (GB) compared with bendamustine alone in patients with rituximab-refractory iNHL (n = 396). Patients in the GB group who had not experienced disease progression at the end of induction received obinutuzumab monotherapy every 2 months for up to 2 years. On the basis of positive results from this study, demonstrating significant improvement in PFS in the GB arm with a median PFS of 29 versus 14 months (hazard ratio [HR], 0.52; 95% CI 0.39, 0.70; p > 0.0001) (Sehn 2015), *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 iNHL (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 4) to cease evaluating obinutuzumab in patients with R/R DLBCL in the expansion phase. Patients with DLBCL enrolled after the identification of the idasanutlin maximum tolerated dose (MTD) in combination with obinutuzumab will instead receive idasanutlin in combination with rituximab.

1.2.2.2 Clinical Safety of Obinutuzumab

As of the safety data cutoff date of *4 July 2016*, an estimated *4,454* patients with CLL or NHL had 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 studies. In Study GAO4768g (evaluating 1,000 mg vs. 2,000 mg of obinutuzumab), 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 studies, but most events occurred in the first cycle. 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 high-dose, NHL cohorts from Study BO20999). In studies of obinutuzumab in combination with either CHOP (Study GAO4915g) or bendamustine (Study BO21000), the incidence of IRRs regardless the relationship with obinutuzumab, was 70%• 78%.

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

1.3 BACKGROUND ON IDASANUTLIN

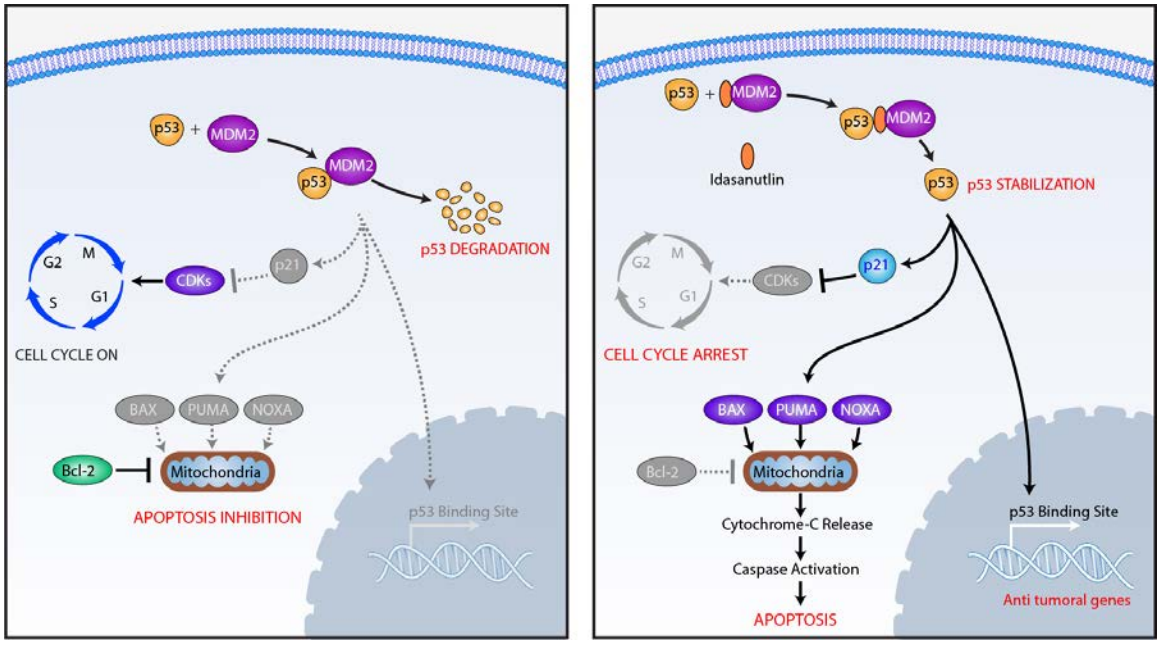
The tumor suppressor p53 plays a pivotal role in protection from cancer development. It is a transcription factor that is activated following stress and regulates multiple downstream genes implicated in cell cycle control, apoptosis, DNA repair, and senescence in non-stressed cells (Ray-Coquard et al. 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 and to restore p53 function (Ray-Coquard et al. 2012). Treatment of cancer cells expressing wild-type 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 expressing wild-type p53 with nutlins stabilizes p53 and 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 imidazoline 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 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 MDM2 protein with high affinity (KD = 5.7 nM) and to inhibit MDM2• p53 binding with IC_{50} of 6.6 ± 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 Nonclinical Experience with Idasanutlin and Obinutuzumab *or Rituximab*

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.

The majority of B-lymphoid malignancies, including NHL and CLL, also express wild-type p53 (Imamura et al. 1994). The non-overlapping and complementary mechanisms of action of obinutuzumab *or rituximab* (direct tumor cell death) and idasanutlin (increased apoptosis) may provide superior efficacy in treating B-lymphoid malignancies.

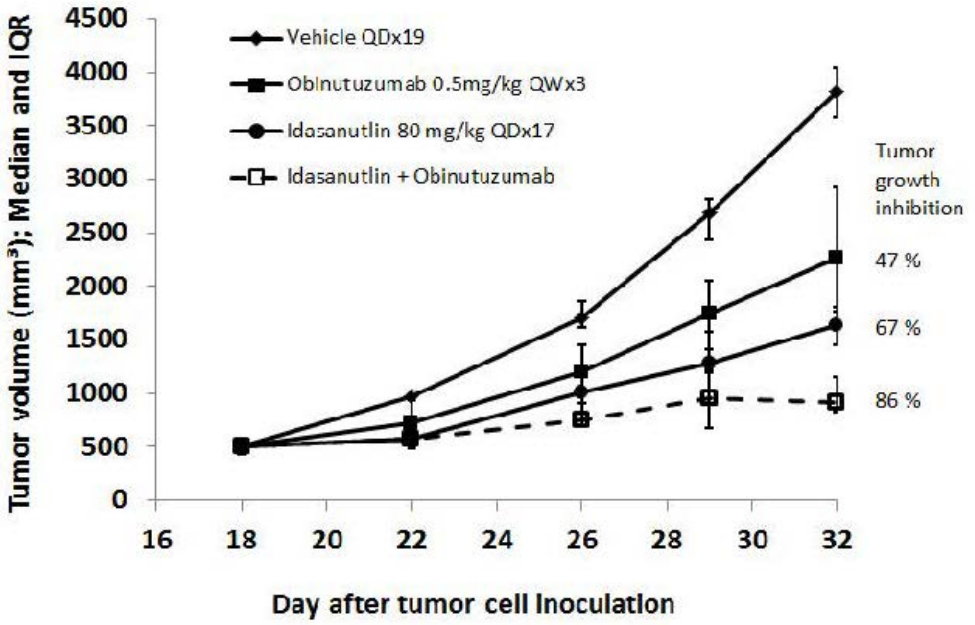
In in vitro assays, idasanutlin induced concentration-dependent apoptosis in a mantle cell lymphoma cell line (Z-138) and in a diffuse large B-cell lymphoma cell line (DOHH-2), and the combination with obinutuzumab further enhanced cell death induction. Importantly, idasanutlin neither influenced obinutuzumab- *or 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-mediated NK cell activation (Herting et al. 2014; Herting et al. 2016).

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

In a Z-138 mantle cell lymphoma xenograft study a suboptimal dose of obinutuzumab showed 47% TGI and idasanutlin monotherapy showed 67% TGI. The combination of obinutuzumab with idasanutlin resulted in superior TGI of 86% compared with single-agent treatment (see Figure 2).

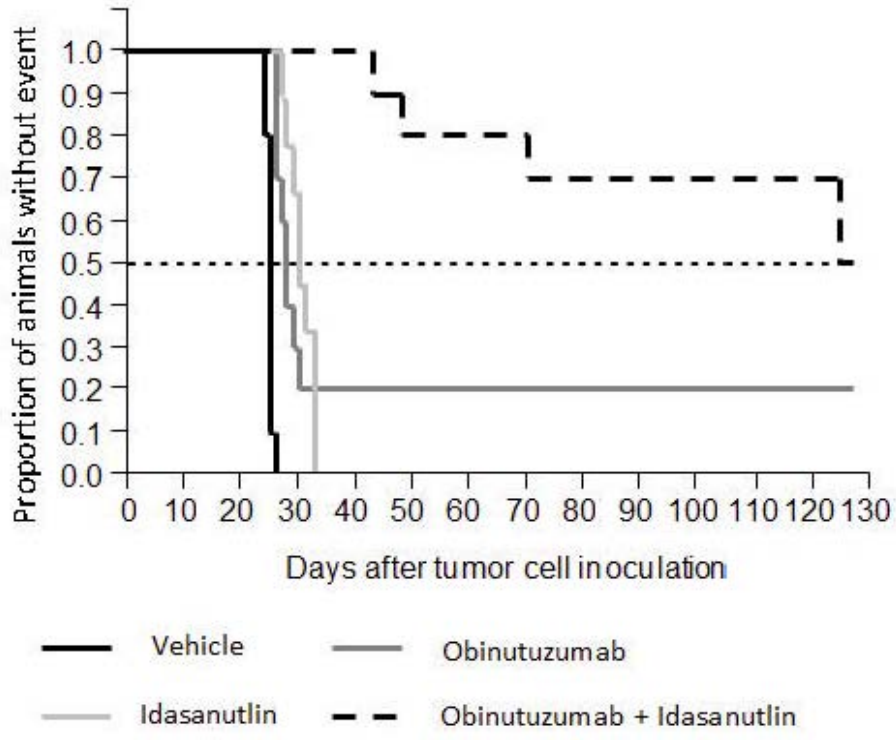
Figure 2 Z-138 MCL Xenograft Model: Tumor Growth Inhibition Analysis



IQR = interquartile range; MCL = mantle cell lymphoma; QD = once daily; QW = once weekly.
Note: Z-138 xenograft study, tumor growth inhibition (TGI) analysis: 10 animals per treatment group, obinutuzumab at a suboptimal dose of 0.5 mg/kg resulted in 47% TGI, idasanutlin at 80 mg/kg resulted in 67% TGI and the combination of obinutuzumab at 0.5 mg/kg with idasanutlin at 80 mg/kg yielded a tumor growth inhibition of 86% on Day 32 after tumor-cell inoculation.

The superiority of the combination treatment in the Z-138 xenograft model was also demonstrated using a time-to-event analysis and resulted in 5 of 10 tumor-free animals on Day 125 (see Figure 3).

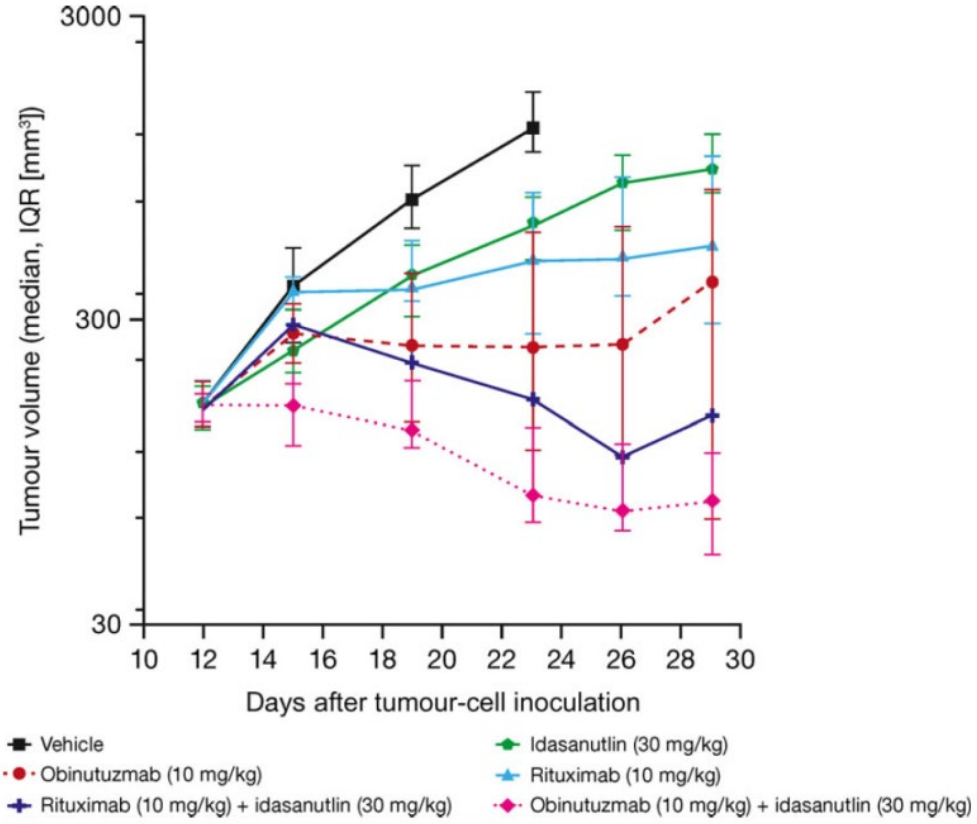
Figure 3 Z-138 Xenograft Model: Time-to-Event Analysis



Note: With 10 animals per treatment group, the combination of obinutuzumab at 0.5 mg/kg with idasanutlin at 80 mg/kg resulted in 50% of animals being tumor-free on Day 125 after tumor cell inoculation.

In an additional in vivo study using the DoHH-2 DLBCL xenograft model, the combination of obinutuzumab *or rituximab* and idasanutlin also resulted in superior efficacy: 94% TGI using a suboptimal dose of obinutuzumab and tumor regression (TGI >100%) using 10 mg/kg of obinutuzumab *and 94% TGI using 10 mg/kg of rituximab* versus the respective monotherapy treatments (see Figure 4).

Figure 4 DoHH-2 DLBCL Xenograft Model: Tumor Volume Analysis



DLBCL = diffuse large B-cell lymphoma; IQR = interquartile range; TGI = tumor growth inhibition.
Note: With 10 animals per treatment group, obinutuzumab at a dose of *10* mg/kg resulted in *91*% TGI, idasanutlin at 30 mg/kg resulted in 56% TGI, *and* rituximab at 10 mg/kg resulted in 72% TGI. *The* combination of obinutuzumab at *10* mg/kg and idasanutlin at 30 mg/kg resulted in *in tumor regression (TGI >100%), and* the combination of rituximab at 10 mg/kg and idasanutlin at 30 mg/kg resulted in *99% TGI.*

Caution should be used when interpreting any mouse toxicology data. It is important to note that none of the mice changed more than 20% of 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* and idasanutlin combination therapy in clinical studies.

1.3.2 Quality Development

Two compounds of the drug family of nutlins binding to an identical binding site have been investigated in clinical studies: RO5045337, a predecessor molecule with lower affinity tested in 350 patients in total and a new version, idasanutlin, which is used in all ongoing and planned studies. Tablets with amorphous compound were originally

developed with a microprecipitated bulk powder (MBP) formulation and used to treat 209 patients in early clinical studies (see Table 1). In an alternative approach to stabilize the amorphous state of the drug substance, a spray-dried powder (SDP) formulation was developed. Pharmacokinetic (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 approach 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.

1.3.3 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, best response observed in relapsed solid tumor patients was stable disease (SD) (RO5045337 Investigator's Brochure).

In the RO5045337 leukemia study (NO21279), 96 patients relapsed or refractory to all available standard-of-care regimens were treated in stratum A (AML, ALL, and 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 [redacted]), and 15 patients showed SD with this early formulation of the MDM2-inhibitor (RO5045337).

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. The patients received treatment for the adverse event and continued study treatment without dose adjustments. No dose-limiting toxicities (DLTs) were reported in 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 daily (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 or complete remission with incomplete platelet count recovery (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 patient 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.

Table 1 Completed, Ongoing, and Planned Idasanutlin Studies

Protocol No.	*Phase, Design*	*Patient Population, No. of Planned Patients*	*Monotherapy/ Combination Therapy*	*Formulation*	*Status*
NP27872 [a]	*Phase I, dose-escalation, food-effect, and biomarker study*	*Solid tumor, n =99 (Dose-escalation cohorts, n =48; Biomarker cohorts, n =37; Food-effect cohorts; n =10; Apoptosis-imaging cohort, n=4)*	*Idasanutlin monotherapy*	*MBP*	*Complete*
NP28679 [b]	*Phase I/Ib, dose-escalation study (Part 1), in combination with cytarabine (Part 2), cytarabine and anthracycline (Part 3), and in combination with cytarabine for PK and safety of optimized SDP (Part 4)*	*AML, n =122 (Part 1 mono DE, n =20; Part 1 mono extension, n =9; Part 2 combo DE, n =23; Part 2 extension, n =38 [n =17 mono, n=21 combo]; Part 3, n =0; Part 4, n =32)*	*Idasanutlin monotherapy and combination therapy with cytarabine• containing regimens*	*Parts 1, 2, 1 extension, 2 extension =MBP; Part 4 = optimized SDP*	*Complete (undergoing CSR preparation)*

Protocol No.	*Phase, Design*	*Patient Population, No. of Planned Patients*	*Monotherapy/ Combination Therapy*	*Formulation*	*Status*
NP28902 [c]	*Phase I, drug-drug interactions with CYP3A4 inhibitor (Part 1), rBA (Part 2), and food effect of optimized SDP (Part 3)*	*Solid tumor, n =61 (Part 1, n =20; Part 2, n =12; Part 3, n =29; Optional extension, n =20)*	*Idasanutlin monotherapy*	*Part 1 =MBP; Part 2 =MBP, optimized MBP, initial SDP; Part 3 = optimized SDP*	*Complete*
WO29519 [d]	*Phase III study in combination with cytarabine*	*AML, n =440*	*Idasanutlin combination therapy with cytarabine*	*Optimized SDP*	*Ongoing*
GH29914 [e]	*Phase Ib/II study of venetoclax in combination with idasanutlin for safety and efficacy*	*AML, Phase Ib (dose escalation)* [f]*; Ven + Idasa: n =up to 54; Phase II (expansion): both arms each, n =10•40*	*Venetoclax combination therapy with idasanutlin*	*Optimized SDP*	*Ongoing*
BH29812 [g]	*Phase Ib/II study to assess safety and efficacy of idasanutlin in combination with obinutuzumab or rituximab*	*Dose-escalation phase: FL and DLBCL, n =9•40* *Expansion phase: FL, n =40 and DLBCL, n =40*	*Idasanutlin combination therapy with obinutuzumab or rituximab*	*Optimized SDP*	*Ongoing*

Protocol No.	*Phase, Design*	*Patient Population, No. of Planned Patients*	*Monotherapy/ Combination Therapy*	*Formulation*	*Status*
NP29910 [h]	*Phase I study to investigate the excretion balance, PK, metabolism, and absolute oral bioavailability of a single oral dose of [^{14}C]-labeled idasanutlin and an intravenous tracer dose of [^{13}C]-labeled idasanutlin in a single cohort of patients with solid tumors*	*Solid tumor, n =8•10*	*[^{14}C]- and [^{13}C]-labeled idasanutlin*	*[^{14}C]-labelled idasanutlin formulation, MBP for oral capsule* *[$_{13}$C]-labeled formulation, intravenous administration*	*Ongoing*

AML =acute myeloid leukemia; Cobi =cobimetinib; combo =combination therapy; CSR =Clinical Study Report; CYP =cytochrome P450; DE =dose escalation; DLBCL = diffuse large B-cell lymphoma; MBP =microprecipitated bulk powder; Idasa =idasanutlin; mono =monotherapy; PK =pharmacokinetic; rBA =relative bioavailability; SDP =spray-dried powder; Ven =venetoclax

[a] *Final data cutoff date, 2 September 2014.*

[b] *Final data cutoff date, 28 August 2016.*

[c] *Final data cutoff date, 19 May 2015.*

[d•h] *Data cutoff date, 13 September 2016.*

[f] *The study also includes a Ven +Cobi arm that is not relevant to idasanutlin development.*

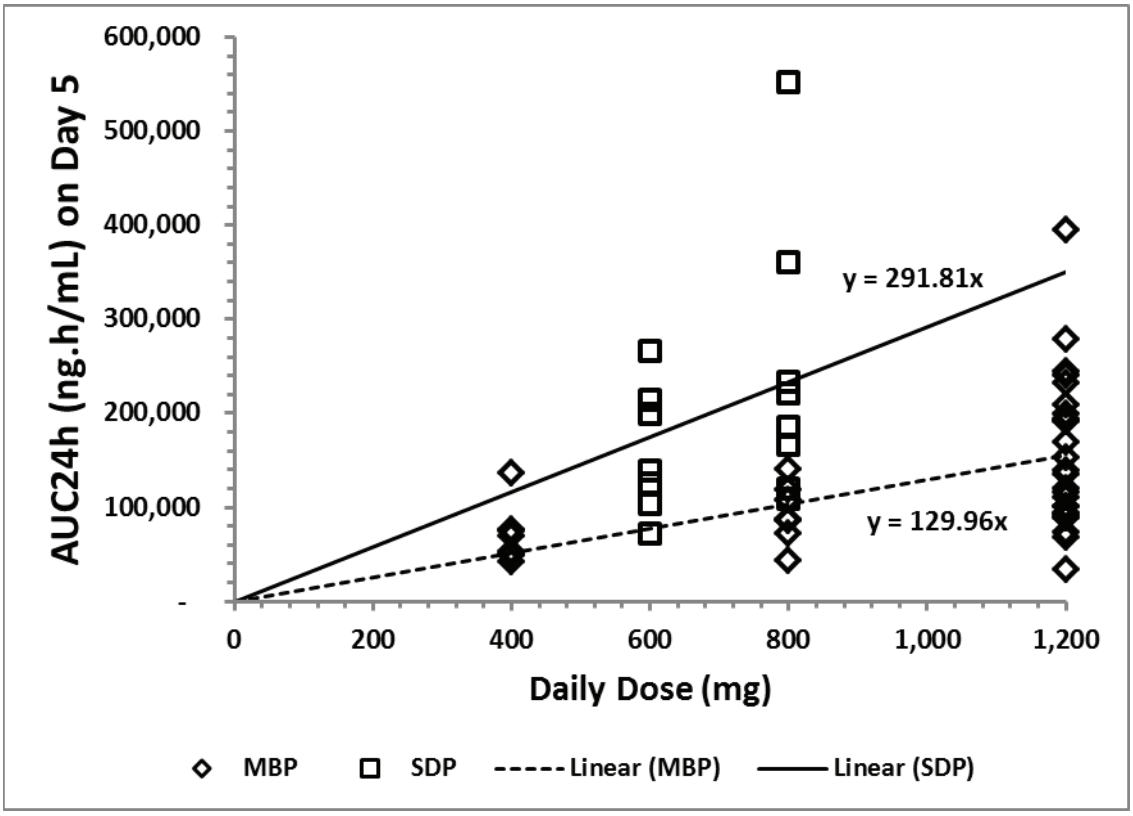
1.3.3.1 Clinical Pharmacology Summary

Clinical Pharmacokinetics

Clinical pharmacokinetics obtained from studies in patients with solid tumors (Studies NP27872 and NP28902) or with AML (Study NP28679) treated with idasanutlin who were dosed at between 100 and 3200 mg daily or QW are summarized as follows:

- Half-life ($t_{½}$) was ~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 $<$30%, and interpatient variability was ~50%.
- East-Asian ethnicity, age, sex, and concomitant cytarabine treatment did not have an apparent impact on PK exposure.
- The SDP formulation was tested in Studies NP28679 and NP28902, and it appears to be twice more bioavailable than the MBP formulation (see Figure 5).
- There was no major effect of low-fat and high-fat meals on pharmacokinetics for the SDP formulation to be used in the current study.
- Idasanutlin is 99.99% protein bound; bone marrow exposure is ~70% of its plasma level at steady state. Idasanutlin and its metabolites are mainly excreted via the hepatic route through bile, with minimal ($<$1%) renal elimination.

Figure 5 Dose Exposure (AUC) SDP versus MBP Formulations in Patients with AML



AML = acute myeloid leukemia; AUC = area under the concentration• time curve; BID = twice a day; MBP = microprecipitated bulk powder; QD = once a day; SDP = spray-dried powder.

Notes: Both MBP and SDP formulations showed a linear dependence of AUC on dose.

Based on slopes, AUC_{24h} was approximately twice as high with SDP than with MBP.

Data were derived from the AML Study NP28679 and application was QD for 400 mg/d and BID for • 600 mg/d.

Clinical Pharmacodynamics

Serum levels of macrophage inhibitory cytokine-1 (MIC-1), a secreted protein that is strongly induced by activated 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.

Drug-Drug Interactions

Idasanutlin is a cytochrome (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 may affect concomitant OATP1B1/3 substrates. These are the basis for the prohibited therapy list for the present study (see Table 10, Table 11, and Table 12; 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 throughout the completion of the ongoing Phase I/Ib study NP28679 in AML.

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 impact on idasanutlin maximum concentration values (C_{max}) but increased AUC values by 32%, which suggests a minimal (no clinically significant) drug-drug interaction (DDI) potential with a single use of a strong/moderate CYP3A4 or CYP2C8 inhibitor *(assuming the same minimal effect, as the two isozymes have the metabolic pathway for idasanutlin)*. However, a concomitant second strong/moderate inhibitor of the other CYP pathway (e.g., adding CYP2C8 *inhibition* to CYP3A4 *inhibition*) may increase idasanutlin exposure to a clinically significant level. Because some NHL patients receive strong/moderate CYP3A4 inhibitors for prophylactic or treatment purpose, in this protocol CYP2C8 inhibitors will be prohibited to prevent double-blockade DDI. UGT1A3 may be a major clearing enzyme *for idasanutlin*; its strong inhibitor gemfibrozil is also a CYP2C8 inhibitor that will be excluded from the current study.

As idasanutlin is a substrate for both CYP3A4 and CYP2C8, the known inducers of CYP3A4 and CYP2C8 will also be prohibited from the current study to prevent loss of exposure for idasanutlin.

There is no relevant DDI expected between the two combined drugs *(neither between rituximab and idasanutlin nor between obinutuzumab and idasanutlin)* in the present study. No correlation was apparent between idasanutlin plasma concentration and QTcF.

See the idasanutlin Investigator's Brochure (IB) for additional details on nonclinical and clinical studies.

1.3.3.2 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 (Final Date 2 September 2014; 99 patients) and Study NP28902 (cutoff 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 as the most common adverse events. Grade 3• 5 adverse events were frequently reported in 63.6% of patients with solid tumors treated with idasanutlin in Study NP27872, most commonly from blood and lymphatic system disorders, gastrointestinal disorders, and metabolism and nutrition disorders System Organ Class (SOC).

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 anti-diarrheal treatments for subsequent cycles.

Serious adverse events were reported in 32 of 99 patients in Study NP27872, most commonly thrombocytopenia, febrile neutropenia, neutropenia, anemia, and leukopenia. The most frequently reported serious adverse events in Study NP28902 in 16 of 61 patients were pyrexia, cellulitis, and dehydration. Overall, 7 deaths in Study NP27872 and 3 deaths in Study NP28902 were reported. Of the 7 deaths reported in Study NP27872, 5 were attributed to disease progression, 1 was due to intraabdominal hemorrhage with pulmonary embolism (unrelated), and 1 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. The cause of death for the other patient in Study NP28902 was pneumonia aspiration, considered 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, of which *16* deaths were associated with or resulted from adverse events. Of the *8* 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) 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. 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 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 these 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 for first-line treatment of patients with B-cell NHL, FL and DLBCL remain an area of high medical need in which novel targeted therapies are required to improve patient outcome (see Section 1.1).

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 (Section 1.2.2.1).

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 1,920 mg/m^2. In total, 15 patients had stable disease and 1 patient with [redacted] achieved a PR and continued on 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 with 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 in safety pattern for patients treated with the 400- and 500-mg Days 1• 5 BID MBP formulation could be detected compared with that in the solid tumor patients (see Section 1.3.3.2). The main DLTs were thrombocytopenia and neutropenia.

However, based on the fact that the majority of B-lymphoid malignancies, including NHL and CLL, express wild-type p53 and the complementary mechanisms of action involving increased apoptosis (MDM2 antagonists) or direct cell death (obinutuzumab *or rituximab*), the combination of *MDM2 antagonists and obinutuzumab or rituximab* has the potential for superior efficacy *compared to single-agent treatment* in treating B-lymphoid malignancies. The different mechanisms of action (anti-CD20) and two different "late-merging" apoptosis pathways further reduce likelihood of (early) resistance.

In vivo, the combination of obinutuzumab *or rituximab* with the MDM2 inhibitor idasanutlin resulted in robust combined anti-tumor efficacy in p53 wild-type xenograft models (Z-138 and DoHH). These preclinical data strongly support the investigation of obinutuzumab *or rituximab* and idasanutlin as combination therapy in clinical studies for CLL and follicular NHL and DLBCL (Herting et al. 2014; Herting et al. 2016).

Although there is potential of overlapping toxicity with regard to bone marrow suppression *(*anemia, neutropenia, and thrombocytopenia*;* see Table 14) between obinutuzumab *or rituximab* and idasanutlin, the Grade • 3 adverse event rates of hematological 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 a potential delay plan are in place, despite the low starting dose for idasanutlin.

In summary, Study BH29812 has been designed to explore different doses of idasanutlin in combination with a fixed dose of obinutuzumab *or rituximab* in patients with R/R FL and DLBCL*, respectively*, with the primary objective to determine the MTD in combination with obinutuzumab *for R/R FL and the MTD in combination with rituximab for R/R DLBCL* and the response rates in addition to safety, pharmacokinetics, and exploratory PD parameters in Phase II. 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.

With the below mentioned risk-minimization measures in place (see Section 5.1), the benefit• risk is considered acceptable for the use of idasanutlin in combination with obinutuzumab *or rituximab* in this Phase Ib/II study (see Table 17 ,Table 18, Table 19, and Table 20).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of obinutuzumab in combination with idasanutlin in patients with *R/R FL and rituximab in combination with idasanutlin in patients with R/R DLBCL.* 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*,* idasanutlin*,* and *rituximab).*

2.1 SAFETY OBJECTIVES AND ENDPOINTS

The safety objectives for this study are as follows:

- To determine the recommended Phase II dose (RP2D) for idasanutlin when given in combination with a fixed dose of obinutuzumab *or rituximab* on the basis of the incidence of DLTs during the *DLT windows (see Section 3.1.2.1)* of study treatment
- To evaluate the safety and tolerability of obinutuzumab *or rituximab* in combination with idasanutlin, including DLTs, on the basis of the following endpoints:

  Nature, frequency, severity, and timing of adverse events

  Changes in vital signs, electrocardiograms (ECGs), and clinical laboratory results during and following study treatment administration

2.2 EFFICACY OBJECTIVES

The objective will be assessment of response 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 5), hereinafter referred to as *modified* Lugano 2014 criteria. Response will be determined by an Independent Review Committee (IRC) and by the investigator.

2.2.1 Primary Efficacy Objective and Endpoint

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

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

2.2.2 Secondary Efficacy Objectives and Endpoints

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

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

2.2.3 Exploratory Efficacy Objective and Endpoints

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of obinutuzumab in combination with idasanutlin *in R/R FL and rituximab in combination with idasanutlin in R/R DLBCL* 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 (expansion only)

- PFS
- EFS
- Disease-free survival (DFS)
- OS
- Additional descriptive analysis based on TP53 status will be performed on the following endpoint:
  - CR at EOI, as determined by the IRC on the basis of PET-CT scans

2.3 PHARMACOKINETIC OBJECTIVES AND ENDPOINTS

The PK objectives for this study are as follows:

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

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

2.4 BIOMARKER OBJECTIVES AND ENDPOINTS

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

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

  Non-inherited biomarkers from tumor tissue samples and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL *(see* Table 13*)*

  Non-inherited biomarkers *from serum and whole blood*:

  MIC-1

  Circulating lymphoma cells

  Cell-free circulating tumor DNA

  Lymphocyte immunophenotyping

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 idasanutlin in combination with obinutuzumab in patients with R/R FL *and rituximab in combination with idasanutlin in 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 RP2D for idasanutlin *in combination with obinutuzumab for FL and in combination with rituximab for DLBCL. Dose escalation starts with idasanutlin* in combination *with obinutuzumab in all patients (FL and DLBCL) until the MTD (Regimen A)* (see Section 3.1.2) followed by*:*

- *Dose confirmation and potential dose escalation in DLBCL patients for idasanutlin in combination with rituximab to determine the RP2D for this combination.*

- *Dose confirmation and potential dose escalation in FL patients for a different regimen (Regimen B, obinutuzumab given alone in Cycle 1 followed by*

idasanutlin and obinutuzumab in combination from Cycles 2 to 6) to determine the RP2D for this regimen.

RP2D(s) and regimens for FL and DLBCL will be decided at the end of dose-escalation phase, and two different RP2Ds and/or regimens may apply for FL and DLBCL, respectively.

In the expansion phase, patients with FL will receive idasanutlin at the RP2D of the selected regimen (A or B) in combination with obinutuzumab, and patients with DLBCL will receive idasanutlin at the RP2D in combination with rituximab.

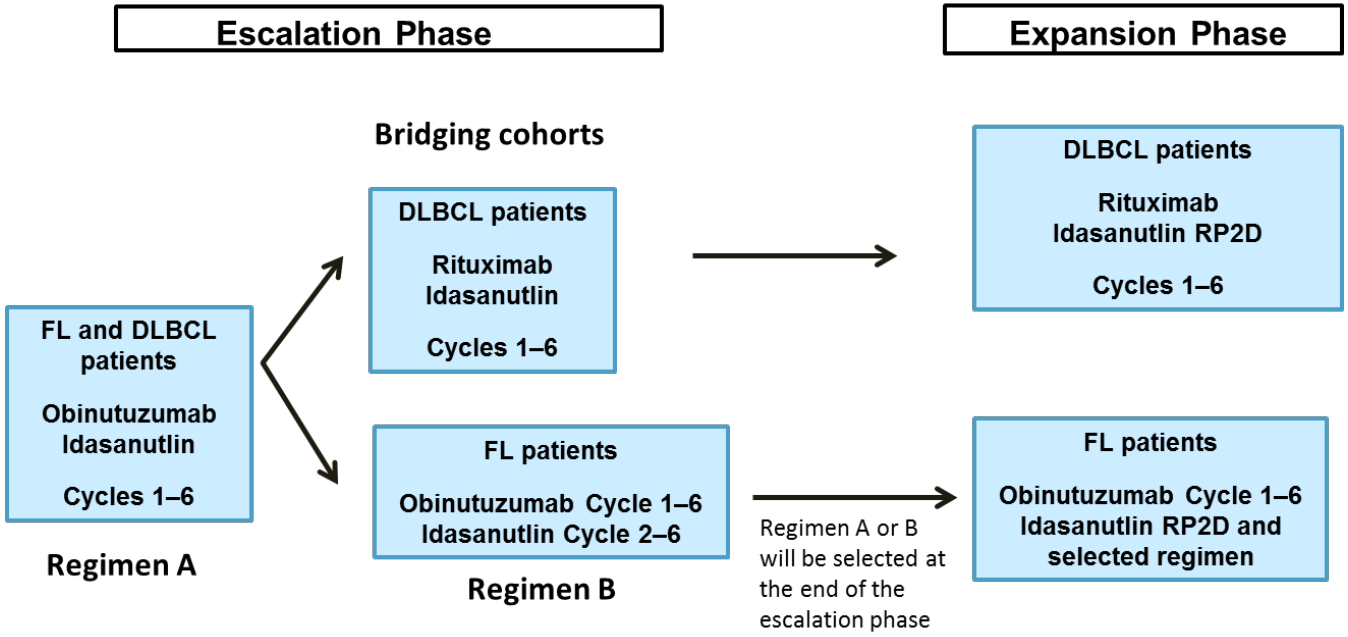
Patients with R/R FL enrolled in the dose-escalation phase may be eligible to receive post-induction treatment (referred to as maintenance) with obinutuzumab (see Section 3.1.2.2 and Section 3.1.3 for details on treatment regimens).

Patients with R/R FL enrolled in the expansion phase may be eligible to receive maintenance treatment with obinutuzumab 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 expansion phase may be eligible to receive post-induction treatment (referred to as consolidation) with rituximab and idasanutlin (see Section 3.1.3 for details on treatment regimens).

A study schema is provided in Figure 6. Refer to Sections 3.1.2 and 3.1.3 for details on the treatment regimens.

Figure 6 Study Schema



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

Overall, approximately 89• 120 patients with R/R FL and DLBCL are expected to be enrolled in this study at approximately 25 investigative sites around the world.

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

Response will be determined by the IRC (see Section 3.1.4) and the investigator using slightly modified Lugano 2014 criteria requiring normal bone marrow for PET-based CR if bone marrow was positive at baseline (see Appendix 5). 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 assessments are provided in Appendix 1 and Appendix 2; the schedule for PK assessments is presented in Appendix 3.

3.1.2 Dose-Escalation Phase (Part 1)

The purpose of the dose-escalation phase (Part 1) is to identify the RP2D *and regimen* for idasanutlin when combined with a fixed dose of 1000 mg of obinutuzumab in patients with R/R FL and *the RP2D for idasanutlin when combined with 375 mg/m² of rituximab in patients with R/R* DLBCL. The RP2D will be based on MTD of idasanutlin when combined with a fixed dose of obinutuzumab *or with 375 mg/m² of rituximab,* but will also include all safety data during treatment. *There could be two different RP2Ds and/or regimens dependent on the combinations of idasanutlin plus obinutuzumab or idasanutlin plus rituximab.*

During the escalation phase, approximately 9• 40 patients will be enrolled in dosing groups of 3• 6 patients each and will be treated at escalating doses of idasanutlin in accordance with the treatment regimen and dose-escalation rules described in Section 3.1.2.2.

Patients will be closely monitored for adverse events during a DLT assessment window, defined as the first treatment cycle *for Regimen A and the first two treatment cycles (one cycle of idasanutlin combination treatment) for patients enrolled in bridging cohort(s) in which idasanutlin will start at Cycle 2 (Regimen B). See Section 3.1.2.2 for treatment regimens.* Adverse events meeting the criteria for DLT, as defined below (see Section 3.1.2.1), will be reported to the Sponsor within 24 hours (see Section 5.4.2).

Patients experiencing a DLT during the *DLT window* 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 who has not been previously treated in the study. Patients who miss one or more doses of obinutuzumab*, rituximab,* or idasanutlin during the DLT assessment window for reasons other than a DLT will also be replaced.

3.1.2.1 Definition of Dose-Limiting Toxicity

In this study, a DLT is defined as at least one of the following events occurring during the first cycle *(or the first two cycles in the bridging cohorts for patients with FL who start idasanutlin at C*ycle 2*)* of treatment and assessed by the investigator as not clearly 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
- 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 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
- *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 (according to Hy's Law) and will be considered a DLT*
- 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 $>$5 days) or a documented infection

  Grade 4 neutropenia lasting $>$7 days

  Grade 3 or 4 thrombocytopenia *if associated with Grade ≥ 3 bleeding*

  Grade 4 thrombocytopenia lasting $>$7 days

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

Induction treatments will be administered in 28-day cycles, as outlined in Table 2. Intrapatient dose escalation is not permitted in this study. The starting dose for idasanutlin will be 100 mg QD. The dose for idasanutlin will be increased by at least 50 mg from the preceding dose level. *During the dose-escalation phase, patients will be enrolled according to the schema in Figure 6. 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 defined DLT window before enrollment commences in the next cohort.*

Patients in the first cohort will begin with a starting oral dose of 100 mg of idasanutlin QD on Days 1•5 of each cycle in combination with a flat dose of obinutuzumab 1000 mg intravenous (IV) on Days 1, 8, and 15 of Cycle 1 and Day 1 of Cycles 2•6 (see Table 2 and Figure 11 for details on treatment regimens). This regimen is referred to as Regimen A.

Following the identification of the MTD for idasanutlin in combination with obinutuzumab, a bridging cohort of DLBCL patients will be opened to test this MTD in combination with rituximab (375 mg/m^2 on Day 1 of each cycle; see Figure 6, Figure 12, and Table 2).

If safety and tolerability allow, idasanutlin dose escalation may be explored in combination with rituximab in patients with DLBCL until identification of a new MTD (see Figure 6). A different RP2D in combination with rituximab maybe chosen based on a different MTD.

Following the identification of the MTD for idasanutlin in combination with obinutuzumab, a bridging cohort of FL patients will be opened to test this MTD in a different regimen, referred to as Regimen B. Obinutuzumab will be given alone in Cycle 1 and in combination with idasanutlin in Cycles 2•6 (see Figure 6, Figure 12, and Table 2).

If safety and tolerability allow, idasanutlin dose escalation may be explored with this Regimen B in patients with FL until identification of a new MTD (see Figure 6). The RP2D and regimen for patients with FL will be decided at the end of the dose-escalation phase. Two different RP2Ds and/or regimens may apply for FL and DLBCL, respectively.

After the last patient in each cohort has completed the DLT observation period, the Sponsor, in consultation with the investigators, will evaluate the next dose recommended according to the modified continual reassessment method with overdose control (mCRM; see Section 3.1.2.3) and agree on doses for the subsequent cohort,

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, de-escalated, or an additional cohort at the same dose level may be enrolled.

During the dose-escalation phase, study treatment will be administered as outlined in Table 2. Patients with FL who achieve a CR or PR at the EOI will also receive maintenance treatment with obinutuzumab. 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 (see Table 3).

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.

Table 2 Induction Treatment for Dose-Escalation Phase

	Dose-Escalation*, FL and DLBCL Patients* (28-Day Cycles): *Regimen A*
Cycle 1	DLT period • Obinutuzumab 1000 mg IV on Days 1, 8, and 15 • Idasanutlin, oral Days 1• 5, starting dose 100 mg QD, minimal clinically and pharmacologically feasible dose-escalation steps 50 mg
Cycles 2• 6	• Obinutuzumab 1000 mg IV on Day 1 • Idasanutlin, oral Days 1• 5, starting dose 100 mg QD
	Dose-Escalation Bridging Cohort, DLBCL Patients Only (28-Day Cycles)
Cycle 1	*DLT period* • *Rituximab 375 mg/m² IV on Day 1* • *Idasanutlin, oral Days 1•5, starting dose MTD identified in combination with obinutuzumab with Regimen A, minimal clinically and pharmacologically feasible dose-escalation steps 50 mg*
Cycles 2–6	• *Rituximab 375 mg/m² IV on Day 1* • *Idasanutlin, oral Days 1•5, starting dose MTD identified in combination with obinutuzumab*
	Dose-Escalation Bridging Cohort, FL Patients Only (28-Day Cycles): Regimen B
Cycle 1	• *Obinutuzumab 1000 mg IV on Days 1, 8, and 15*
Cycles 2–6	• *Obinutuzumab 1000 mg IV on Day 1* • *Idasanutlin, oral Days 1•5, starting dose MTD identified in combination with obinutuzumab with Regimen A during dose escalation, minimal clinically and pharmacologically feasible dose-escalation steps 50 mg*
	DLT period will be Cycles 1 and 2.

DLBCL =diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; *FL =follicular lymphoma;* IV=intravenous; *MTD =maximum tolerated dose;* QD=once a day.

Table 3 Maintenance Treatment during the Dose-Escalation Phase for Patients with Follicular Lymphoma

	Post-Induction Treatment
Patients with FL	*Maintenance treatment consisting of the following:* • *Obinutuzumab 1000 mg IV every 2 months for 24 months*

FL = follicular lymphoma; IV = intravenous.

3.1.2.3 Dose-Toxicity Model with mCRM

The dose escalation will employ a modified-Continual Reassessment Method with Overdose Control (mCRM) design in order to define MTD and/or the recommended dose. The design is based on the primary safety variable (the occurrence of a DLT). The MTD is defined as the dose that maximizes the probability of a DLT being in the targeted toxicity interval of 25%• 35%, subject to the probability of DLT being in the excessive toxicity interval of 35%• 100% being less than 35%. Patients within a cohort will be enrolled in a sequential manner in cohorts of at least 3 patients each, which, if required, can be expanded with additional patients. Each patient will be observed over 1 cycle (1 cycle lasts 28 days) of treatment for DLT assessment. The first patient in each cohort will be observed for safety for 1 week *after Cycle 1, Day 1* before enrolling additional patients in the cohort. After the last patient in each cohort has completed the 1-cycle DLT observation period, the Sponsor and investigators will evaluate the next dose recommended by the mCRM design and agree on the dose for the subsequent cohort. At each dose-escalation step, the dose can be escalated, de-escalated, or an additional cohort at the same dose-level can be enrolled.

The starting dose for idasanutlin will be 100 mg and the fixed dose for obinutuzumab will be 1000 mg. *The dose for rituximab starting from the bridging cohort for DLBCL patients will be 375 mg/m^2.* The dose-escalation is for the dose of idasanutlin. The maximum allowable increments for idasanutlin between dose levels will be as follows:

- 151% increase if the last idasanutlin dose is below or equal to 300 mg
- • 33% of relative increase if the last idasanutlin dose is above 300 mg

The dose of idasanutlin 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 dose increments. Clinical judgment will always override mCRM recommendations in the dose-selection process.

The model-based dose escalation at each step will identify the next recommended dose level subject to the following criteria:

- The posterior probability of being within the excessive toxicity interval (above 35% DLT probability) is below 35%, and
- The posterior probability of being within the target toxicity interval (of 25%• 35% DLT probability) is maximized.

Note: To fulfill the above statement, a loss function is being defined as per following:

- 0• 25 under dosing
- 25• 35 targeted toxicity
- 35• 60 excessive toxicity
- 60• 100 unacceptable toxicity

  Where the “under dosing” and “excessive toxicity” are identically weighted to weight as much as the “unacceptable toxicity”; as such, the “targeted toxicity” will be maximized (i.e., Loss=[1,0,1,2]).

The dose-escalation will stop under the following circumstances:

- The maximum sample size of 40 patients has been reached, or
- At least a minimum of 9 patients across 3 cohorts has been accrued overall, at least 6 patients have been accrued at the MTD dose, and in addition the probability that the MTD dose lies within the target toxicity interval is above 40%.

The dose-toxicity relationship is described by a two-parameter logistic regression model:

$$logit\left[p\left(d_j^*\right)\right] = \log(\alpha) + \beta d_j^*$$

where $p\left(d_j^*\right)$ denotes the probability to experience a DLT at dose d_j (mg), where $d_j^* = \log(\frac{d_j}{d^R})$ is the transformed (i.e., standardized) dose using the reference dose, $d^R = 300$.

The following bivariate log normal prior distribution will be used for α and β assuming no prior correlation between model parameters:

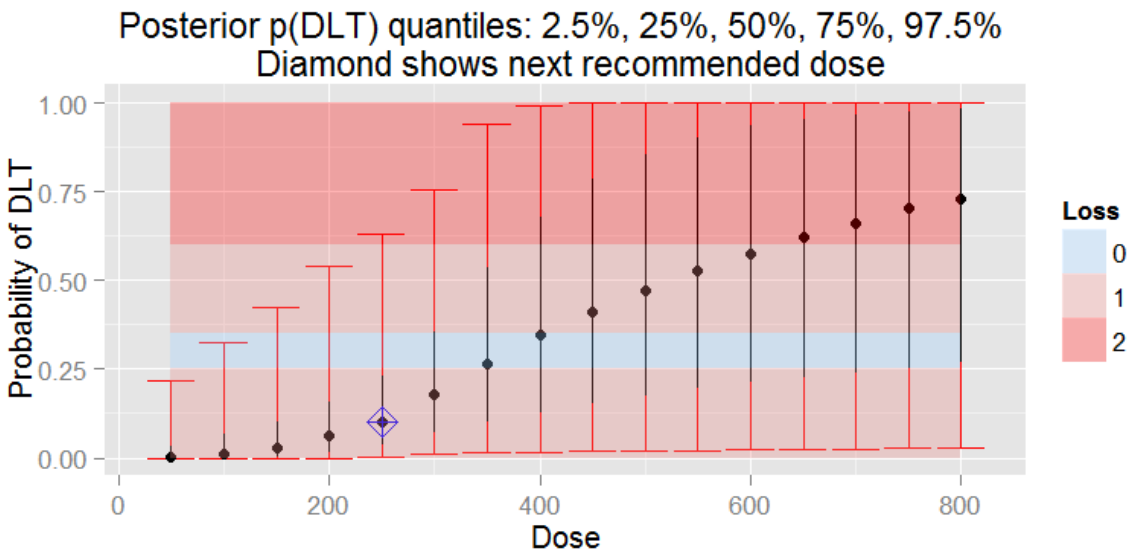
$$\begin{bmatrix}\log(\alpha)\\ \log(\beta)\end{bmatrix} \sim \mathcal{N}\left[\begin{pmatrix}-1.237\\ 0.460\end{pmatrix}, \begin{pmatrix}2.661 & 0\\ 0 & 1.816\end{pmatrix}\right]$$

A graphical representation based on this prior model is shown in Figure 7 and has been constructed to match the skeleton of probability shown in Table 4. This skeleton is based on a model built on an existing study (Study NP27872) and represents the most up-to-date relationship between dose and toxicities.

Table 4 Initial Skeleton of Prior Guesses

Dose (mg)	50	100	150	200	250	300	350	400	450	500	550	600	650	700	750	800
Prior guess of risk (%)	3	8	15	22	30	38	45	52	58	65	68	71	74	77	79	82

Figure 7 Illustration of Model for the mCRM Design at Study Start (3 Patients Recruited at 100 mg without DLT).



DLT = dose-limiting toxicity; mCRM = modified continual reassessment method with overdose control.

The prior model can be characterized as follows: based on the initial skeleton of prior guesses, the a priori MTD point estimate is 250 mg; this is the dose with the highest probability to have a DLT probability in the target interval of 25%–35%. After 3 patients were recruited at 100 mg without DLT, the recommended dose (after an update) is 250 mg. Furthermore, it is illustrative to consider various hypothetical trial realizations. If 3 patients are given the starting dose 100 mg and none of them develop a DLT, then the next mCRM dose recommendation is 250 mg. Afterwards the mCRM recommendations are 300 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 600 mg, 700 mg, and 800 mg if the next cohorts of 3 patients also have no DLT observed each time. The increase is a bit faster (not exceeding the maximum increments specified above) if more patients are enrolled into the cohorts. For example, if the cohorts are made with 6 patients rather than 3, all without DLTs, the dose recommended for the sequence of cohorts is 100 mg, 250 mg, 300 mg, 300 mg, 350 mg, 400 mg, 600 mg,

750 mg, and 800 mg. On the other hand, if DLTs are observed, the next recommended dose is (almost) equal to or lower than the current dose. Specifically, if in the first cohort at 100 mg with 3 patients when 1, 2, or 3 DLTs are observed, then the dose recommended for the second cohort is 100 mg, 50 mg, or 50 mg, respectively. If the first DLTs are observed in the second cohort of 3 patients at 250 mg and none in the first cohort of 100 mg, the dose for the third cohort is recommended as 250 mg, 200 mg, and 100 mg when 1, 2, or 3 DLTs are observed. A summary of the subsequent recommendation among same principle is provided in Table 5.

Table 5 Hypothetical Trial Realization (Cohort Size = 3)

Observation of First DLT at	Recommended Dose among the Number of DLT Effectively Observed		
	1 DLT	2 DLTs	3 DLTs
100 mg	100 mg	50 mg	50 mg
250 mg	250 mg	200 mg	100 mg
300 mg	300 mg	250 mg	250 mg
300 mg	300 mg	300 mg	300 mg
350 mg	350 mg	300 mg	300 mg
400 mg	400 mg	350 mg	350 mg
450 mg	450 mg	400 mg	400 mg
500 mg	500 mg	450 mg	450 mg
600 mg	650 mg	550 mg	500 mg
750 mg	800 mg	650 mg	600 mg

DLT = dose-limiting toxicity.

After each cohort of patients completes dosing, the posterior distribution of the model parameters of the logistic regression model will be updated with the observed DLT occurrence data and, hence, an estimate of the next dose, or declaration of MTD, will be derived. In addition relevant demographic, adverse event, laboratory, dose administration, and PK (if available) data will be reviewed. Then, subject to clinical judgment, a new cohort of patients will be dosed at the next recommended estimate of the MTD or the highest allowable dose based on the pre-specified over-dose constraints, whichever is lower. The design will continue as described, assigning patients to the MTD as estimated from all of the DLT data cumulatively, until one of the predefined stopping criteria is satisfied or the predetermined sample size of DLT-evaluable patients is reached, whichever comes first. *The above described mCRM algorithm will be first used for predicting the MTD in the combined FL/DLBCL dose-escalation cohorts where idasanutlin is given in combination with obinutuzumab. A similar mCRM will be then employed to support dose escalation in the DLBCL bridging cohorts where idasanutlin is given in combination with rituximab and in the FL bridging cohorts in which idasanutlin is given in combination with obinutuzumab using Regimen B, if applicable.*

With the end of the mCRM phase, a tentative MTD estimate is defined. Moreover, the recommended dose will be defined by taking into consideration all available data gathered so far.

3.1.3 Expansion Phase (Part 2)

The expansion phase is designed to further assess the safety and efficacy of obinutuzumab in combination with idasanutlin at the RP2D *with the selected regimen in patients with R/R FL and of rituximab in combination with idasanutlin at the RP2D in patients with R/R DLBCL.* Approximately 80 patients (40 patients with R/R FL and 40 patients with R/R DLBCL) will be enrolled during the expansion phase and treated as described below. *The start of the expansion phase may not happen simultaneously for the two indications.*

All patients will receive 6 cycles of induction treatment, administered in 28-day cycles, as outlined in Table 6. Patients with FL who achieve a CR *or* PR at the EOI will receive maintenance treatment with obinutuzumab *and idasanutlin. Patients with DLBCL who achieve a CR or PR at the EOI will receive consolidation treatment with rituximab 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 7).*

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 schedules of assessments are provided in Appendix 1 and Appendix 2, and a study schema is provided in Figure 6.

Table 6 Induction Treatment for the Expansion Phase

	Induction Treatment (28-Day Cycles)	
Patients with FL	***Regimen A*** [a] ***Obinutuzumab plus idasanutlin from Cycles 1•6***	***Regimen B*** [a] ***Obinutuzumab at Cycle 1 and obinutuzumab plus idasanutlin from Cycles 2•6***
Cycle 1	• Obinutuzumab 1000 mg IV on Days 1, 8, and 15 • Idasanutlin, oral, Days 1• 5, RP2D *in combination with obinutuzumab* [a]	• *Obinutuzumab 1000 mg IV on Days 1, 8, and 15*
Cycles 2• 6	• Obinutuzumab 1000 mg IV on Day 1 • Idasanutlin, oral, Days 1• 5, RP2D *in combination with obinutuzumab*	• *Obinutuzumab 1000 mg IV on Day 1* • *Idasanutlin, oral, Days 1•5, RP2D in combination with obinutuzumab*
Patients with DLBCL		
Cycles 1•6	• *Rituximab 375 mg/m² IV on Day 1* • *Idasanutlin, oral, Days 1•5, RP2D in combination with rituximab*	

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

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

Table 7 Post-Induction Treatment for the Expansion Phase

	Post-Induction Treatment
Patients with FL	*Maintenance treatment consisting of the following:* • *Obinutuzumab 1000 mg IV every 2 months for 24 months* • *Idasanutlin for 6 months* [a]
Patients with DLBCL	*Consolidation treatment consisting of the following:* • *Rituximab 375 mg/m² IV every 2 months for 6 months* • *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 Roche 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 at regular intervals during the study. 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 and bone marrow biopsy results. 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 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 new anti-lymphoma treatment every 3 months until the end of the study. Details are provided in the schedules of assessments (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 maintenance treatment, and
- All enrolled patients with DLBCL have been followed for at least 1 year after they have completed or discontinued study treatment (including induction treatment and consolidation treatment, as applicable).

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 48 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Treatment Combination

MDM2 regulates p53 through a negative feedback loop. However, in cancer cells overexpressing MDM2, this feedback loop is dysregulated. 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).

A class of imidazoline compounds was identified as potent and selective inhibitors of the p53-MDM2 interaction (Vassilev et al. 2004). These molecules, termed nutlins, interact specifically with the p53-binding pocket of MDM2, and, thus, free p53 from negative feedback mechanisms. Idasanutlin binds selectively to the p53 site on the surface of the MDM2 molecule in vitro with high affinity and can effectively displace p53 from MDM2, leading to stabilization and accumulation of p53 protein and activation of the p53 pathway. The compound has good oral bioavailability and has shown TGI in two different NHL mouse xenograft models tested at doses that did not cause noteworthy toxicity. However, its efficacy as a monotherapy in these mouse models is very inferior to combination with other drugs, especially obinutuzumab.

Obinutuzumab *and rituximab have* been shown to be safe and active as monotherapy in patients with R/R NHL (Section 1.2.2).

Based on the fact that the majority of B-lymphoid malignancies, including NHL and CLL, bear wild-type p53, and the complementary mechanisms of action involving increased apoptosis (MDM2 antagonists) or direct cell death (obinutuzumab *and rituximab*), the combination of *an anti-CD20 antibody (obinutuzumab or rituximab) and a MDM2 antagonist* has the potential for superior efficacy *compared to single-agent treatment* in treating B-lymphoid malignancies. The combination of obinutuzumab *or rituximab* with the MDM2-antagonist idasanutlin resulted in enhanced cell death of p53 wild-type NHL tumor cells. Therefore, the complementary mechanism of actions of these drugs promises additive effect and, there are first attempts to quantify cooperative effects in system biology based PD model. In fact, combinatorial efficacy of different pro-apoptotic drugs in NHL can be described in a quantitative way by a signaling model of CD20 pharmacodynamics (Harrold et al. 2012).

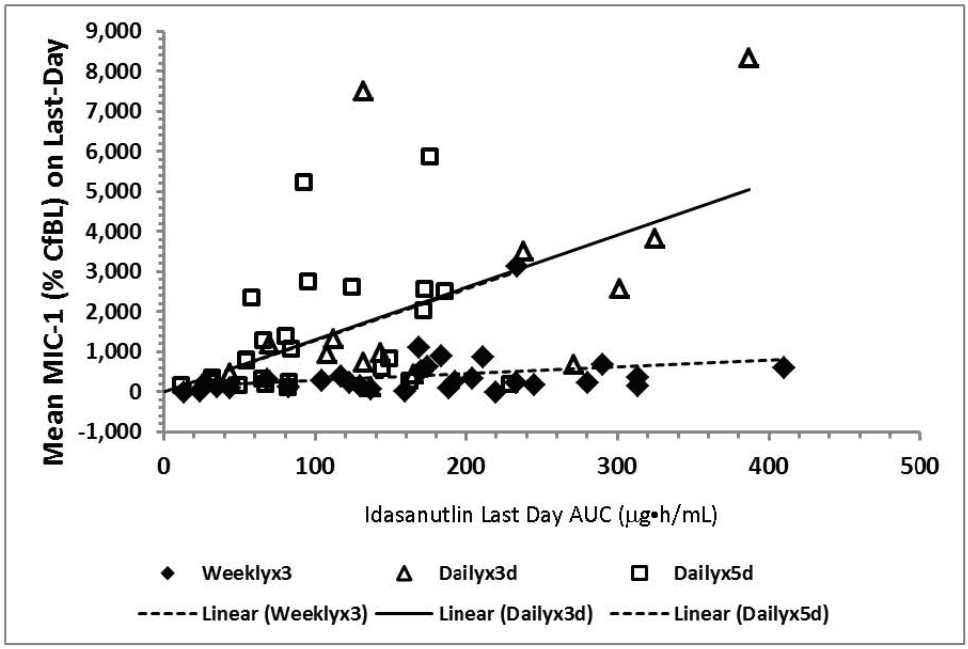
A xenograft model of MCL shows more durable response only in idasanutlin in combination with the anti-CD20 drug obinutuzumab (see Section 1.3.1, Figure 2). The addition of obinutuzumab or rituximab to idasanutlin may primarily prevent relapse. Enhanced tumor control in the Z-138 MCL and a high bar DLBCL xenograft model was observed with an obinutuzumab *or rituximab* plus idasanutlin combination over idasanutlin monotherapy *or an anti-CD20 antibody alone* (see Section 1.3.1). These data support further evaluation of the combination of idasanutlin and obinutuzumab *or rituximab* in clinical studies in lymphoma.

3.3.2 Rationale for Idasanutlin Starting Dose

Based on data from Studies NP27872 and NP28679 in solid tumors and AML, the first PD signal was detected at an AUC_{24} between 50 and 60 • g • hr/mL. For the QD • 5 days regimen (see Figure 8), 55 • g • hr/mL (55,000 ng • hr/mL) corresponds to a daily dose of

approximately 100 mg of the idasanutlin SDP formulation, which is equivalent to 200 mg of the MBP formulation (see Figure 5 for conversion).

Figure 8 PD Biomarker Defines Doublet Starting Dose of Idasanutlin (MBP)



AUC = area under the concentration time• curve; d = day; MIC-1 = macrophage inhibitory cytokine 1; MBP = microprecipitated bulk powder; PD = pharmacodynamic.

In addition, safety data are available for patients with solid tumors and NHL who received the idasanutlin MBP formulation. For the 200-mg MBP QD • 5 schedule, no Grade 3 or 4 hematologic or related gastrointestinal toxicities were observed.

Therefore, a daily dose of 100 mg of the idasanutlin SDP formulation, which is roughly the equivalent of 200 mg idasanutlin MBP formulation, seems to be a safe starting dose with potential to activate p53 as determined by the MIC-1 PD Marker in combination with obinutuzumab *or rituximab*.

3.3.3 Rationale for Dosing Regimen

There is a standard regimen for obinutuzumab used in all pivotal NHL studies of a fixed dose of 1,000 mg (see the Obinutuzumab Investigator's Brochure) in combination with several cytotoxic drugs. These data support this efficacious fixed dose as the basis for combinations of obinutuzumab with targeted drugs. Obinutuzumab at a fixed dose of 1,000 mg is also being studied in combination with other targeted agents in a number of ongoing clinical studies, including MPDL3280A (GO29383), polatuzumab vedotin (GO27834), and venetoclax (GP28331, GO27878).

The study will start with obinutuzumab standard dosing in combination with idasanutlin from Cycles 1 to 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 from Cycles 2 to 6 will be explored (bridging cohorts) 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 on Day 1 in subsequent cycles. Those 3 doses of obinutuzumab, when combined with idasanutlin at higher doses in the same treatment cycle, may induce more profound hematologic toxicities. Staggered idasanutlin 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.

The dose of rituximab of 375mg/m^2 is the recommended dose in the NHL population and is the standard of care. For DLBCL patients 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). The dose and schedule in the consolidation phase will be 375 mg/m^2 every 2 months in combination with idasanutlin to explore potential benefit with consolidation treatment. 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.

Idasanutlin MBP-formulation PK exposure, PD effects (e.g., MIC-1, as 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 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.

The MTD for solid tumors, including patients with NHL, has been determined as 500 mg BID • 3 days or 500 mg QD • 5 days with MBP formulation. The QD • 3 days dose regimen did not achieve steady-state exposure in solid tumors, and NHL achieved a clinically relevant shorter period of SD but did not alleviate thrombocytopenia. Since a relatively low dose is to be initiated, QD of two 50-mg tablet has been chosen. As the dose escalation increases, the “pill burden” may require BID administration beyond the 400-mg QD dose SDP formulation for dose escalation.

The PK results from SDP food-effect study of 19 evaluable patients in Study NP28902 (all patients received three crossover treatments) showed that there was little evidence for a food effect. For the high-fat meal, there was equivalence demonstrated in all PK exposure parameters analyzed with 90% CI values, while the low-fat meal demonstrated $<$20% increase in all PK exposure parameters analyzed and were just outside the upper limit of 90% CI for bioequivalence. However, this increase is unlikely to be clinically

significant as the interpatient PK variability regardless of food is approximately 50%. As such, patients will take idasanutlin with their own choice of fed or fast.

3.3.4 Rationale for Pharmacokinetic Assessments

The PK data are important to meet at least three major objectives: to support dose escalation, to assess potential PK interactions between idasanutlin and obinutuzumab *or rituximab*, and to explore exposure-effect (including PD, efficacy, and adverse events) relationships. The data from the current study may be combined for further analysis (e.g., popPK) with those generated from other studies.

3.3.5 Rationale for PET-CT–Defined Complete Response as the Primary Efficacy Endpoint

In DLBCL, the prognostic value of the post-treatment fluorodeoxyglucose (^{18}F-FDG) PET-CT scan has been well documented (Thomas et al. 2010; Vitolo et al. 2010). PET-CT scans have been implemented in the Lugano 2014 criteria (Cheson et al. 2014) and are commonly used to assess efficacy in medical practice and clinical studies 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 immunochemotherapy showed, with a median follow-up of 55 months, a 4-year PFS in PET-CT• positive and PET-CT• negative patients of 23.2% (95% CI: 11.1%, 37.9%) versus 63.4% (95% CI: 55.9%, 70.0%; $p < 0.001$), respectively, and a 4-year survival of 87.2% (95% CI: 71.9%, 94.5%) versus 97.1% (95% CI: 93.2%, 98.8%; $p < 0.0001$), respectively (Trotman et al. 2014). In the relapsed FL setting, results from a preliminary analysis of a Phase II study (BO21003) comparing obinutuzumab versus rituximab monotherapy demonstrated that the post-induction PET-CT status is strongly prognostic of PFS. With a median follow-up of 32.1 months, the risk of disease progression was significantly reduced in PET-CT• negative compared with PET-CT• positive patients, regardless of the assessment criteria: either International Harmonization Project criteria (hazard ratio [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 and CT scan results for lymphoma staging and response assessment (Lugano 2014 criteria; Cheson et al. 2014).

3.3.6 Rationale for Biomarker Assessments

3.3.6.1 Rationale for Analysis of Known Prognostic Factors: 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 the GCB subgroups demonstrating a better 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 shown that *BCL2* is the most mutated gene in patients with GCB DLBCL, observed in up to 35% of cases (Schuetz et al. 2012). Approximately 9%• 17% of patients with newly diagnosed DLBCL harbor an underlying *MYC* rearrangement, and these patients are at high risk of treatment failure with R-CHOP (Savage et al. 2009). A subset of patients with *MYC*-positive DLBCL also harbors an additional *BCL2* rearrangement. These "double-hit" lymphomas are associated with a very poor outcome (Savage et al. 2009; Dunleavy et al. 2014). Overexpression of Bcl-2 and Myc in DLBCL has also been observed in the absence of translocation. This "double-positive" DLBCL status is also associated with worse prognosis (Green et al. 2012; Johnson et al. 2012; Hu et al. 2013).

3.3.6.2 Rationale for p53 and Pharmacodynamic Marker Assessments

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 that conveys activatable 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). Further, MDM2 status is important with regards to ability to activate p53 because MDM2 is overexpressed in a wide variety of hematological malignancies, for instance, in approximately 50% of 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, 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 in the response to treatment with idasanutlin and obinutuzumab.

MDM2 mRNA expression in blood appeared to be associated with clinical response in the Phase I study NO21279 in AML with RO5045337; however, the association is not sufficiently robust to use *MDM2* alone for selection of responsive patients. Gene expression signature(s) may provide a means of predicting patient response to MDM2 inhibitors. A signature of four genes (including *MDM2, BBC3/PUMA, XPC,* and

CDKN2A) appears to be associated with response to 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 signature is ongoing in Phase I studies and a planned Phase III AML study of idasanutlin. Analysis of this four-gene signature in NHL-derived tumor tissue may be predictive of 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.

MIC-1, a secreted protein that is strongly induced by activated 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). Therefore, MIC-1 may have utility as a PD biomarker for idasanutlin. In Study NO21279, evaluating RO5045337, which included patients with AML and patients in the AML Phase I study NP28679 for idasanutlin, MIC-1 expression has been shown to be a useful PD biomarker correlating with exposure.

Ongoing evaluation of PD biomarker activity in 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).

3.3.6.3 Rationale for Assessment of Minimal Residual Disease

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 depth of response and monitor patients for possible disease recurrence.

In FL, MRD at end of treatment is likely to be prognostic (Ladetto et al. 2014). In DLBCL, serum MRD was shown to predict early and late progression after first-line treatment (Roschewski et al. 2014). In addition, MRD assessment may complement the response assessment, particularly in immune treatment• based regimens, and mitigate potential false• positive fluorodeoxyglucose (FDG)-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 EOI to allow for an evaluation of the depth of response, and during Maintenance

treatment to allow for an evaluation of long-term response or possible disease recurrence.

4. MATERIALS AND METHODS

4.1 PATIENTS

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

4.1.1 Inclusion Criteria (Escalation and Expansion)

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 6)
- Patients with R/R FL after treatment with at least two prior lines of therapy, including at least one chemoimmunotherapy regimen that contained an anti-CD20 monoclonal antibody and for which no other more appropriate treatment option exists as determined by the investigator
- R/R 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 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 or magnetic resonance imaging [MRI] scan)
- Availability of a representative tumor specimen and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL. Further details are provided in Section 4.5.6.

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

  If a patient has had anti-lymphoma therapy between the time of the prior biopsy and treatment initiation, a repeat biopsy is highly encouraged.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 18 months after the last dose of study treatment

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

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

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

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

  With female partners of childbearing potential (and not using effective contraception), men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 3 months after the last dose of study treatment. Men must refrain from donating sperm for the same period.

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

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

4.1.2 Exclusion Criteria

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

- Known CD20 negative status at relapse/progression
- Central nervous system lymphoma or leptomeningeal infiltration
- 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 • 2 (according to the NCI CTCAE, v4.0) prior to Day 1 of Cycle 1
- Grade 3b follicular lymphoma
- History of transformation of indolent disease to DLBCL
- Treatment with systemic corticosteroids > 20 mg/day prednisone or equivalent

  Patients receiving corticosteroids • 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.
- *Treatment with the following agents within 7 days prior to the first dose of idasanutlin:*

  CYP2C8 inhibitors including gemfibrozil (also a UGT1A3 inhibitor)

  CYP2C8 substrates

  OATP1B1/3 substrates
- *Treatment with the following agents within 14 days prior to the first dose of idasanutlin:*

  Strong CYP3A inducers including rifampin (also a CYP2C8 inducer)
- *Chronic use of CYP2C8 or OATP1B1/3 substrates*
- Clinical conditions requiring treatment with oral or parenteral anticoagulants/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).
- Patients that may refuse blood products and/or have 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,* or idasanutlin formulations
- Active bacterial, viral, fungal, or other infection

  Caution should be exercised when considering the use of obinutuzumab *or rituximab* in patients with a history of recurring or chronic infections.
- Positive for hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), or hepatitis C virus (HCV) antibody at screening
- Known history of HIV positive status

For patients with unknown HIV status, HIV testing must be performed at screening if not in contradiction with local legislation.

- History of Progressive Multifocal Leukoencephalopathy (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 • 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), significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm), or uncontrolled gastrointestinal conditions such as irritable bowel syndrome or Crohn's Disease)
- 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 • 10^9/L

  Platelet count $<$ 75 • 10^9/L
- Any of the following abnormal laboratory values (unless due to underlying lymphoma):

  Creatinine $>$1.5 • the upper limit of normal (ULN) (unless creatinine clearance is normal) or calculated creatinine clearance $<$ 40 mL/min (using the Cockcroft-Gault formula; see Appendix 10)

  AST or ALT $>$ 2.5 • ULN

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

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

  PTT or aPTT $>$ 1.5 • ULN in the absence of a lupus anticoagulant
- Pregnant, lactating, or intending 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
- Unable to comply with the study protocol, in the investigator's judgment

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a Phase Ib/II, open-label, multicenter, non-randomized study of obinutuzumab in combination with idasanutlin in patients with *R/R FL and obinutuzumab or rituximab in combination with idasanutlin in patients with R/R* DLBCL. During the dose-escalation phase, patients with R/R FL or DLBCL will be assigned to dosing groups through an interactive voice or Web-based response system (IxRS). *Following determination of the MTD of idasanutlin in combination with obinutuzumab, bridging cohort(s) of DLBCL patients will be opened to confirm the MTD of idasanutlin in combination with rituximab. Following determination of the MTD of idasanutlin in combination with obinutuzumab, bridging cohort(s) of FL patients will be opened to explore a different regimen (Regimen B, obinutuzumab alone at Cycle 1 and obinutuzumab in combination with idasanutlin at Cycles 2 to 6).* During the expansion phase, patients with *R/R FL* will be treated at the RP2D of idasanutlin plus 1000 mg obinutuzumab *with the selected regimen, and patients with R/R DLBCL will be treated at the RP2D of idasanutlin plus 375 mg/m² rituximab.*

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

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Obinutuzumab

Obinutuzumab will be supplied by the Sponsor as an investigational medicinal product (IMP). Obinutuzumab will be provided as a single-dose, sterile liquid formulation in a 50-mL glass vial containing 1000 mg of obinutuzumab. For information on the formulation and handling of obinutuzumab, see the Obinutuzumab Investigator's Brochure.

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 by the Sponsor as an IMP. Four different film coated tablets with 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 as well as for the market in a dose proportional way with respect to the tablet kernel. The film coated tablets contain RO5503781-020 (spray dried powder consisting of 50% [w/w] RO5503781 and 50% [w/w] copovidone), microcrystalline cellulose, croscarmellose sodium, crospovidone, colloidal silicon dioxide, magnesium stearate, and a film coat. The film coating mixture of Ro 550-3781/F17 (50 mg) and Ro 550-3781/F16 (200 mg) consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide red, and iron oxide black. The film coating mixture of Ro 550-3781/F13 (300 mg) consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol and talc, and the one of Ro 550-3781/F14 (400 mg) consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

All excipients used in the tablet formulations are widely used in pharmaceutical preparations and are of compendial grade.

Film coated tablets of idasanutlin should be stored under the recommended storage conditions, “Do not store above 25°C.”

4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized in Table 6, Figure 6, and Section 3.1.

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

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

4.3.2.1 Obinutuzumab

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

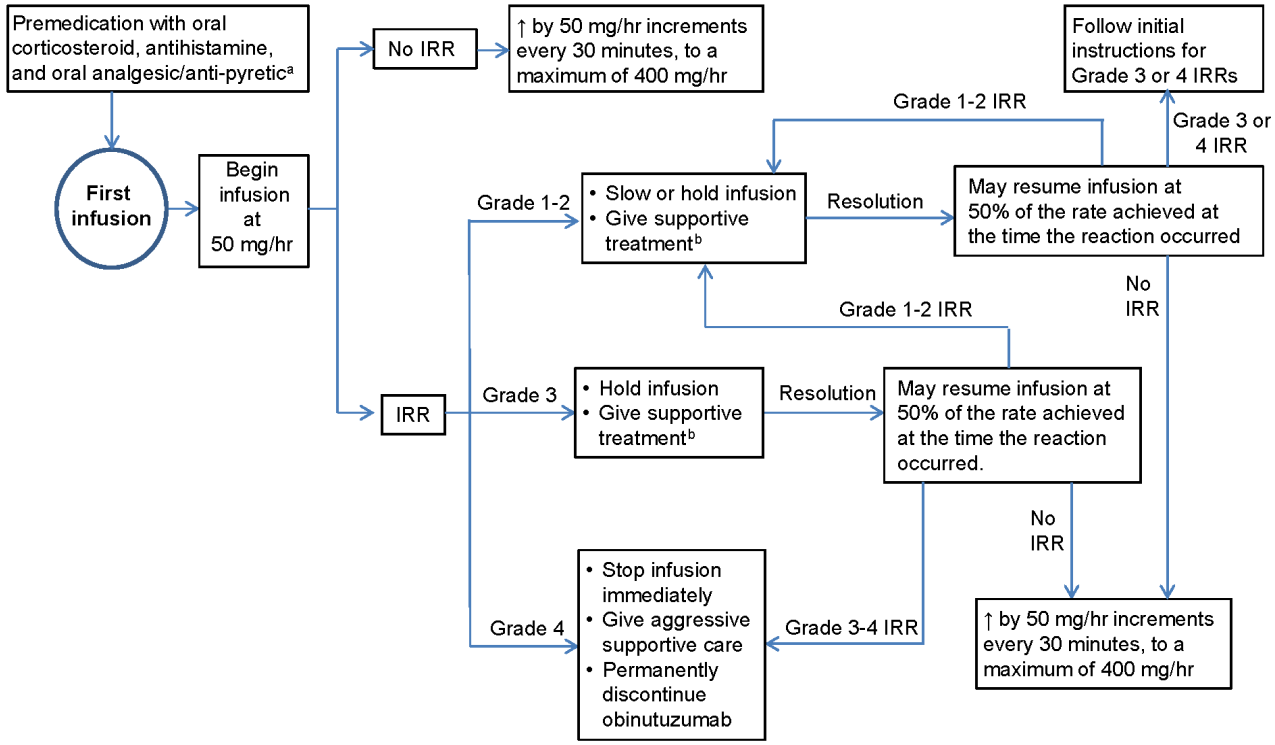
Obinutuzumab should be administered independent of oral application of idasanutlin as an IV infusion through a dedicated line in an environment in which full resuscitation facilities are immediately available and under the close supervision of an experienced

physician. Obinutuzumab infusions will be administered according to the instructions outlined in Figure 9 and Figure 10. For patients with bulky lymphadenopathy, the infusion may be given extremely slowly over a longer period of time, or the dose may be split and given over more than 1 day.

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

Premedication with a corticosteroid, antihistamine, and analgesics or antipyretic agents, as outlined in Section 4.3.2.6, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautious, see Appendix 9.

Figure 9 Guidelines for Obinutuzumab Infusion: First Infusion

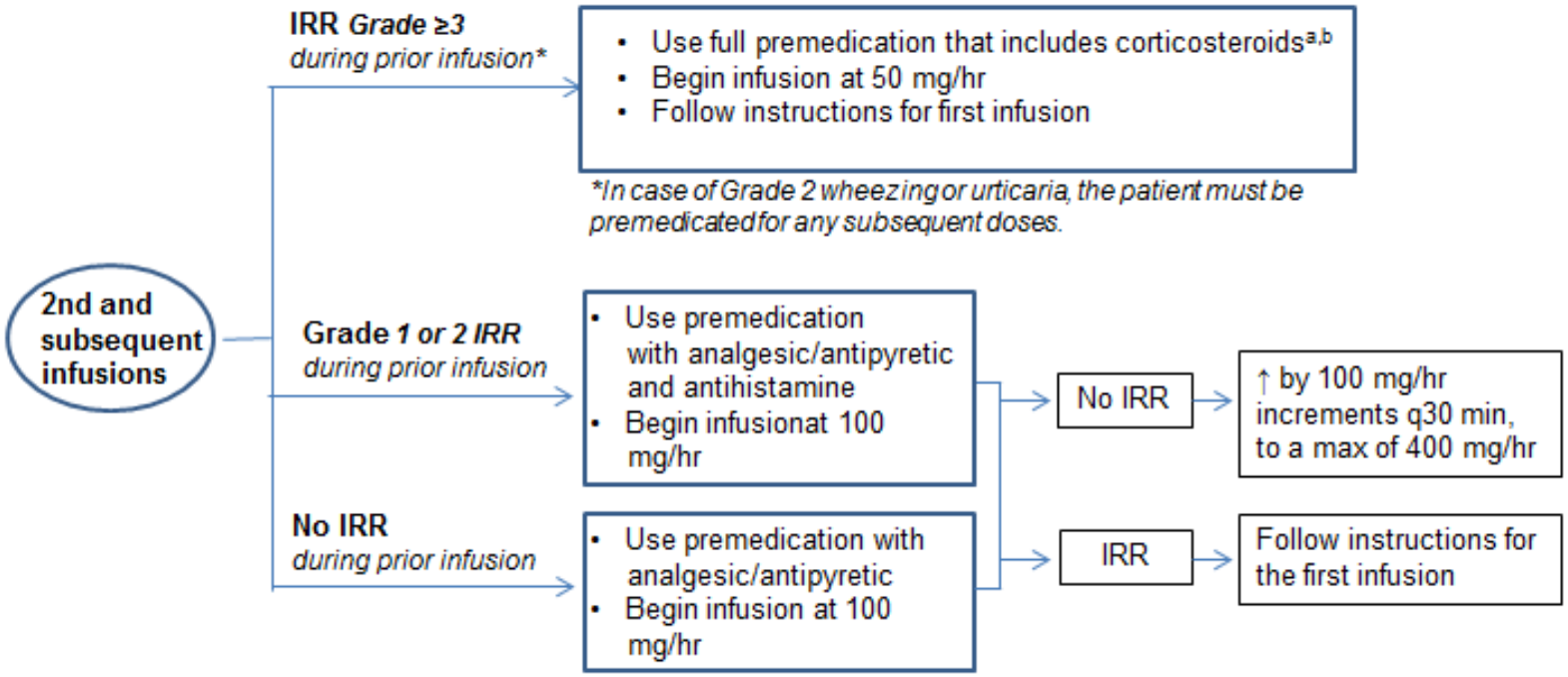


IRR = infusion-related reaction.

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

[b] Supportive treatment should include acetaminophen/paracetamol and an antihistamine such as diphenhydramine, if not administered within the previous 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg oral prednisone or equivalent), and/or bronchodilators. For anaphylaxis precautions, see Appendix 9.

Figure 10 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/anti-pyretic 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 Idasanutlin

Study patients will self-administer idasanutlin tablets orally each day with their own choice of fed or fast.

On days when both idasanutlin and obinutuzumab are given, the order of study treatment administration will be idasanutlin followed by obinutuzumab. 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 where 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. 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.

4.3.2.3 *Rituximab*

Rituximab will be administered by IV infusion at a dose of 375 mg/m² on Day 1 of Cycles 1−6 during induction treatment and 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 • 30 kg/m²), 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 4.3.2.6) and at the first infusion rate (see Table 8).

Rituximab infusions will be administered according to the instructions in Table 8.

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

Rituximab should be administered as a slow IV infusion through a dedicated line. After the end of the first infusion, the IV line or central venous catheter should remain in place for • 2 hours in order to administer IV drugs, if necessary. If no adverse events

occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed.

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.

No dose modification for rituximab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.5.

Premedication with a corticosteroid, analgesic/antipyretic, and antihistamine, as outlined in Section 4.3.2.6, is required to reduce the incidence and severity of IRRs. For anaphylaxis precautions, see Appendix 9.

Table 8 Administration of First and Subsequent Infusions of Rituximab

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

First Infusion (Day 1 of Cycle 1)	*Subsequent Infusions*
	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.

4.3.2.4 *Induction Treatment with Obinutuzumab or Rituximab and Idasanutlin*

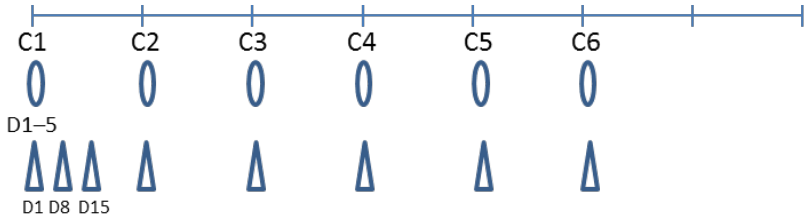
Patients will receive 6 cycles of induction treatment consisting of obinutuzumab or rituximab and idasanutlin as outlined in Table 6. For patients with FL enrolled in the bridging cohort(s), obinutuzumab will be given alone at Cycle 1, and the obinutuzumab and idasanutlin combination will be given from Cycles 2 to 6.

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

Please refer to Section 3 for further details.

Figure 11 Treatment with Idasanutlin and Obinutuzumab: Schedule of Treatment

Regimen A: Idasanutlin plus obinutuzumab in escalation phase (excluding FL bridging cohorts) and expansion phase if Regimen A is chosen:



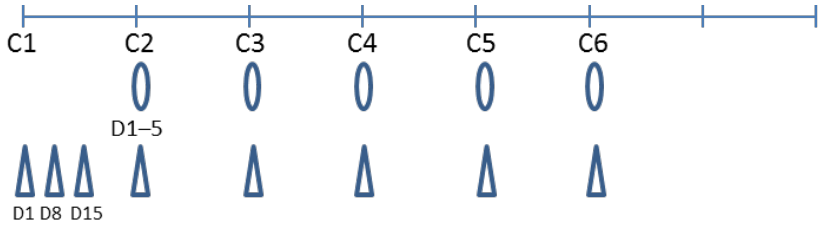
Obinutuzumab: 1000 mg IV on Day 1, 8, 15 of Cycle 1, then Day 1 of each Cycle 2–6

Idasanutlin: QD on D1–5 (BID with daily doses of 400 mg and beyond)

Patients will receive study treatment every 28 days for up to 6 cycles.

BID = twice a day; C = cycle; D = day; IV = intravenous; QD = once a day.
Note: Patients will receive study treatment every 28 days for up to 6 cycles.

Regimen B: Idasanutlin plus obinutuzumab in FL bridging cohorts and expansion phase if Regimen B is chosen:



Obinutuzumab: 1000 mg IV on Day 1, 8, 15 of Cycle 1, then Day 1 of each Cycle 2–6

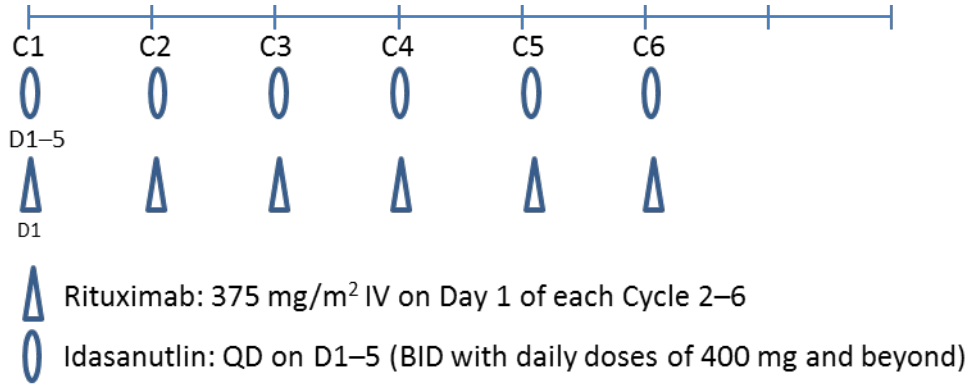
Idasanutlin: QD on D1–5 (BID with daily doses of 400 mg and beyond)

Patients will receive study treatment every 28 days for up to 6 cycles.

BID = twice a day; C = cycle; D = day; IV = intravenous; QD = once a day.
Note: Patients will receive study treatment every 28 days for up to 6 cycles.

Figure 12 Escalation Phase (DLBCL Bridging Cohort[s]) and Expansion Phase with Idasanutlin and Rituximab: Schedule of Treatment

Idasanutlin plus rituximab regimen:



BID = twice a day; C = cycle; D = day; IV = intravenous; QD = once a day.
Note: Patients will receive study treatment every 28 days for up to 6 cycles.

4.3.2.5 *Post-Induction* Treatment for Patients with FL *and DLBCL*

Please refer to Section 3 for further details.

4.3.2.6 Premedication

Patients should receive premedication as outlined in Table 9.

Table 9 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] • Oral analgesic/anti-pyretic [c]	Administer • 30 minutes prior to obinutuzumab *or rituximab* infusion.
	• Patients at risk for TLS (e.g., because of bulky disease or renal impairment [creatinine clearance < 70 mL/min])	• Allopurinol or suitable alternative such as rasburicase, along with adequate hydration	Administer prior to obinutuzumab *or rituximab* infusion.
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 [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]* • *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 • Patients with bulky disease	• Oral corticosteroid [a]	Administer • 1 hour prior to obinutuzumab *or rituximab* infusion.
		• Antihistamine drug [b] • Oral analgesic/anti-pyretic [c]	Administer • 30 minutes prior to obinutuzumab *or rituximab* infusion.
	• Patients still at risk for TLS	• Allopurinol or suitable alternative such as rasburicase, along with adequate hydration	Administer prior to obinutuzumab *or rituximab* infusion.
Cycles 1 to 6	• All patients *receiving idasanutlin*	2nd generation anti-emetics like palonosetron, ondansetron, or granisetron	Administer per individual drug prescribing information

Timepoint	Patients Requiring Premedication	Premedication	Administration
Cycles 1 to 6	• All patients	• No premedication for diarrhea • If diarrhea grade 3 or more occurs, loperamide should be given prophylactically for subsequent cycles	

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

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

[b] For example, 50 mg of diphenhydramine.

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

4.3.3 Investigational Medicinal Product Accountability

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

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

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

4.3.4 Post-Study Access to Obinutuzumab*, Rituximab,* and Idasanutlin

Currently, the Sponsor does not have any plans to provide obinutuzumab*, rituximab,* or idasanutlin or any other study treatments or interventions to patients who have completed the study. The Sponsor will evaluate whether to continue providing obinutuzumab*, rituximab,* and idasanutlin in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Website:
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 EOI or at the end of Maintenance *or consolidation* 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 4.3.2.6.

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

During the dose-escalation phase, granulocyte colony-stimulating factor (G-CSF) is not permitted during the first cycle, unless the patient experiences a DLT of neutropenia.

During the expansion phase, G-CSF is permitted as clinically indicated per American Society of Clinical Oncology (ASCO), European Organization for Research and

Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines (Smith et al. 2006) or per each site's institutional standards.

Prophylactic treatment with antibiotics should be administered per standard of care.

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

4.4.2 Prohibited Therapy

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

- 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 5.1.1.3)
- Use of oral or parental anticoagulants/antiplatelet agents (e.g., chronic daily treatment with aspirin [>325 mg/day], clopidogrel, warfarin, systemic low molecular weight heparin (LMWH), or subcutaneous anticoagulant prophylaxis) are prohibited during the study unless treatment can be discontinued 7 days (or 5 half-lives) prior to initiation of study treatment (except used as flushes for indwelling catheters)
- Vaccination with live vaccines is not recommended during treatment with obinutuzumab *or rituximab* and until B-cell recovery.

Idasanutlin is metabolized mainly by 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), it is not a sensitive CYP3A or CYP2C8 substrate as summarized in Section 1.3.3.1 and thus its metabolism* may *only* be affected by concomitant CYP3A *and* CYP2C8 inducers *or dual CYP3A and CYP2C8 inhibition.* Idasanutlin inhibits CYP2C8 metabolism, which may affect concomitant *CYP2C8* substrates, and its M4 metabolite is an organic anion-transporting polypeptide (OATP)-1B1/3 transporter inhibitor that may affect concomitant *OATP1B1/3* substrates. Thus, *in order to prevent undesirable drug-drug interactions,* the use of any *medication listed in Table 10 (CYP2C8 substrates and inhibitors), Table 11 (strong CYP3A inducers), and Table 12 (OATP1B1/3 substrates) are either prohibited during the study within the DLT evaluation window in the escalation phase or allowed after the DLT evaluation window, after washing out in sufficient duration (for inhibitors) or concomitant use with caution (for inducers)in order to prevent undesirable drug-drug interactions.* Note that gemfibrozil is also a UGT1A3 inhibitor that will be excluded from this study and that CYP3A4 inhibitors are not excluded.

Substrates and inhibitors listed in Table 10 and Table 12 must be discontinued 7 days prior to start of study treatment. Inducers listed in Table 11 must be discontinued 14 days prior to start of study treatment.

Table 10 Prohibited CYP2C8 Substrates, Inhibitors, *and Inducers*

Substrates	Inhibitors [a]	*Inducer* [b]
amiodarone amodiaquine	gemfibrozil *(also a UGT1A3 inhibitor)*	*rifampicin*
cerivastatin	monteleukast	
chloroquine ibuprofen	pioglitazone	
lovastatin *montelukast* paclitaxel	quercetin	
pioglitazone repaglinide	rosiglitazone	
rosiglitazone	trimethoprim	
simvastatin torasemide	•	

[a] *When CYP3A inhibitors are in use, concomitant use of idasanutlin with CYP2C8 inhibitors is to be avoided, to prevent idasanutlin exposure elevation with potentially increased toxicities; use an alternative medication that is not an inhibitor. If these CYP2C8 inhibitors 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 idasanutlin is withheld in that cycle. After discontinuation of the CYP2C8 inhibitor, wait for 7 days before restarting idasanutlin treatment.*

[b] *Concomitant use of idasanutlin with the CYP2C8 inducer rifampicin is to be avoided to prevent idasanutlin exposure loss compromising efficacy; consider alternative medications. If a patient requires use of this medication, use with caution and contact the Roche Medical Monitor (refer to Section 5.4.1) for guidance. The inducer is allowed during the study only if the patient has completed the DLT evaluation window (if patient is in a dose-escalation cohort).*

Table 11 Prohibited *Strong* CYP3A4 Inducers

Inducers (Strong) [a]
carbamazepine
cyproterone
efavirenz
enzalutamine
etravirine
mitotane
modafinil
nevirapine
oxcarbazepine
phenobarbital
phenytoin
rifampicin
St. John's wort

[a] *Concomitant use of idasanutlin with strong CYP3A inducers is to be avoided to prevent idasanutlin exposure loss compromising efficacy; consider alternative medications. If a patient requires use of these medications, use with caution and contact the 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).*

Table 12 Prohibited OATP1B1/3 Substrates

OATP1B1/2 Substrates
asunaprevir
atorvastatin
atrasentan
bosentan
cerivastatin
danoprevir
docetaxel
ezetimibe
fluvastatin
fexofenadine
glyburide
irinotecan
nateglinide
olmesartan
paclitaxel
pitavastatin
pravastatin
repaglinide
rifampin
rosuvastatin
simvastatin acid
telmisartan
valsartan

The above 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 medications not listed above.

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

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

4.5 STUDY ASSESSMENTS

See Appendix 1 and Appendix 2 for the overall schedule of activities and Appendix 3 for the PK schedules of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

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

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

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and, within the defined window, may be used as screening and baseline assessments (see Appendix 1 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 time 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 7 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 6)
- Ann Arbor staging (see Appendix 7)

- B symptoms (unexplained fever > 38°C, night sweats, and unexplained weight loss > 10% of body weight over 6 months)
- For patients with FL: Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI2 (see Appendix 8)
- For patients with DLBCL: IPI (see Appendix 8)
- 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, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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

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

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

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressures while the patient is in a seated position. Vital sign measurements will be performed as outlined in the schedules of assessments (see Appendix 1 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 5). 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 5). Additionally, designation of PET-CT• based PR requires that CT-based response criteria for a CR or PR be met in addition to the PET-CT• based response criteria for a PR (see Appendix 5).

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

If bone marrow infiltration is present at screening, a bone marrow biopsy is required at the EOI response assessment for all patients who may have achieved a CR. In patients with a PR and continued bone marrow involvement, a subsequent bone marrow examination may be required to confirm a CR at a later timepoint.

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

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 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)
- Serum chemistry: 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
- • $_2$ 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 of idasanutlin on embryo-fetal development, monthly pregnancy testing is strongly recommended for women of childbearing potential (CTFG 2014)
- 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*

4.5.6.2 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
- Tumor tissue samples and the corresponding pathology report for retrospective central confirmation of the diagnosis of FL or DLBCL. This tissue sample will also be used for exploratory research on candidate biomarkers (see Table 13)

  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, 15• 20 serial, freshly cut, unstained slides accompanied by a punch biopsy may be sent. A tumor block or punch biopsy is

required for construction of a tissue microarray. If less than 15• 20 unstained serial slides are available, the study site should consult the Sponsor (or delegate) regarding the acceptability of a fewer number of slides.

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

If a patient has had anti-lymphoma therapy between the time of the prior biopsy and treatment initiation, a repeat biopsy is highly encouraged.

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.

- Whole blood and serum samples will be collected for exploratory research on candidate biomarkers, including but not limited to those listed in Table 13.

Table 13 Proposed Non-Inherited Biomarkers

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

ABC = activated B cell–like; DBLCL = diffuse large B-cell lymphoma; GCB = germinal-center B cell–like; IHC = immunohistochemistry; MDM2 = murine double minute 2; MRD = minimal residual disease; NK = natural killer.

Note: Exploratory biomarker research may include but will not be limited to the biomarkers listed in this table.

Samples collected for biomarker analyses may be used for exploratory biomarker research, assay development purposes, and additional safety and immunogenicity assessments, as appropriate.

Based on ongoing analysis of data, the Sponsor may choose to stop any analysis, timepoint or sample type if the data does not support a strong scientific justification to continue.

Biological samples will be destroyed within 5 years after the final clinical study report has been completed. Remaining samples will be stored for exploratory research if the patient provides Roche Clinical Repository (RCR) consent.

4.5.7 Electrocardiograms

Single, resting, 12-lead ECG recordings will be obtained 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 patient is receiving a premedication/study drug IV infusion. 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 the patient's permanent study file at the site. The following should be recorded in 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 postdose 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 2 successive ECGs. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, dehydration, co-medications known to prolong the QT interval, severe bradycardia) and provide this information to the eCRF.

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 Samples for Roche Clinical Repository

4.5.8.1 Overview of the Roche Clinical Repository

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

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

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

4.5.8.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.8) will not be applicable at that site.

4.5.8.3 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to obinutuzumab*, rituximab,* and idasanutlin, 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
- Leftover peripheral blood

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.

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

4.5.8.4 Confidentiality

Confidentiality for All Roche Clinical Repository Specimens

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

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

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

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

Additional Confidentiality for Specimens Used for Genetic Research

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens collected for genetic research. Upon receipt by the RCR, specimens for genetic research are "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A “linking key” between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure.

Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

4.5.8.5 Consent to Participate in the Roche Clinical Repository

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

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

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

4.5.8.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study BH29812 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study BH29812.

4.5.8.7 Monitoring and Oversight

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

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

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

Every effort should be made to obtain information on patients who withdraw from the study before the withdrawal. 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. At the time of withdrawal of consent, the patient will be asked if he or she agrees to be followed for survival information. This agreement must be documented 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 (obinutuzumab *or rituximab* and idasanutlin) should be permanently discontinued in patients who experience any of the following:

- 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 per guidelines provided in Section 5.1.5
- Grade • 3 non-hematologic adverse event that has a reasonable possibility of being related to study treatment and is either life threatening or does not resolve to Grade $<$2 within 21 days
- Disease progression
- Pregnancy

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

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

- During the dose-escalation phase (Part 1), patients who discontinue study treatment prior to completing Cycle 1 for reasons other than toxicity will be replaced.
- Patients discontinued 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 obinutuzumab, *rituximab,* and idasanutlin in completed and ongoing studies. The anticipated important safety risks of obinutuzumab, *rituximab, and idasanutlin* are outlined below. Refer to the Obinutuzumab, *Rituximab,* and Idasanutlin Investigator's Brochures for a complete summary of safety information and prescribing information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1). In addition, patients will undergo adequate safety monitoring during the study, as described in this section and in Section 4.5. Guidelines for managing adverse

events, including criteria for dosage modification and treatment delays or discontinuation, are provided in Section 5.1.5.

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, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia), infections (including PML and HBV reactivation), prolonged B-cell depletion, impaired immunization response worsening of preexisting cardiac conditions, gastrointestinal 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. 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 anti-hypertensive 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 9.

5.1.1.2 Tumor Lysis Syndrome

TLS, including fatal events, has been reported with obinutuzumab administration. Patients at risk for TLS (e.g., because of bulky disease or renal insufficiency) should receive adequate hydration and premedication with allopurinol or an alternative uricostatic agent as indicated in Section 4.3.2.6 (see Table 9). Additional guidelines for management of TLS in this study are provided in Section 5.1.5.

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/• L occurring • 28 days after obinutuzumab treatment has been completed or stopped) or prolonged neutropenia (ANC $<$1000 cells/• L 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 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 in Cycle 1. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients should be closely monitored for thrombocytopenia, especially during the first cycle of treatment. 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 (HBsAg negative and HBcAb positive), or in patients who are carriers 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 who are positive for HBsAg and HBcAb are not eligible for enrollment in this study.

John Cunningham (JC) viral infection resulting in PML has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs or symptoms regarded as "cortical" (e.g., aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes but is not limited to consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA). Additional guidelines for medical management of PML in this study are provided in Section 5.1.2.

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 • 10% of patients) based on clinical trial experience. However, serious IRRs are uncommonly reported (occurring in • 1 of 1,000 and < 1 of 100 patients) and are rarely fatal (occurring in • 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 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 5.1.5). 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.

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 Clostridium 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 5.1.5.

5.1.3.5 *Electrolyte Disorders*

Electrolyte disorders (hypercalcemia, hyperkalemia, hypernatremia, hypocalcaemia, hypokalemia, hypomagnesemia, hyponatremia, hyperphosphatemia, and hypophosphatemia) 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 Risk of Overlapping Toxicities

Overlapping toxicities across *idasanutlin and* obinutuzumab are neutropenia and thrombocytopenia (see Table 14). *Overlapping toxicities across idasanutlin and rituximab are neutropenia and thrombocytopenia (see Table 15).*

Table 14 Overlapping Toxicities: Idasanutlin and Obinutuzumab

	Idasanutlin [a] 5-Day Dosing (100• 800 mg/day) (n=34)		Obinutuzumab (n=215) [b]	
Adverse Event	Overall Number of Adverse Events (%)	Grade • 3 Adverse Events (%)	Overall Number of Adverse Events (%)	Grade • 3 Adverse Events (%)
Anemia	24%	24%	16% [c]	3% [d]
Neutropenia	27%	27%	36% [c]	5%• 14% [d]
Febrile neutropenia	12%	12%	5% [d]	3% [c]
Thrombocytopenia	44%	44%	18% [d]	5%• 8% [d]
Diarrhea	74%	9%	5%• 8% [d]	0 [d]
Nausea	74%	12%	5%• 9% [d]	0 [d]
Vomiting	50%	3%	5% [d]	0 [d]
Fatigue	38%	3%	13% [c]	NA

NA = not applicable.

[a] Data from Phase I single-agent idasanutlin study NP27872; all patients were dosed for 5 days.

[b] Data from obinutuzumab monotherapy.

[c] Data from Study BO29563.

[d] Obinutuzumab Investigator's Brochure.

Table 15 Overlapping Toxicities: Idasanutlin and Rituximab

Adverse Event	Idasanutlin [a] 5-Day Dosing (100•800 mg/day) (n =34) Overall Number of Adverse Events (%)	Idasanutlin [a] 5-Day Dosing (100•800 mg/day) (n =34) Grade • 3 Adverse Events (%)	Rituximab (n =356) [b] Overall Number of Adverse Events (%)	Rituximab (n =356) [b] Grade• 3 Adverse Events (%)
Anemia	24%	24%	1%	1%
Neutropenia	27%	27%	11.2%	4.2%
Febrile neutropenia	12%	12%	<1%	<1%
Thrombocytopenia	44%	44%	9.6%	1.7%
Nausea	74%	12%	17.1%	0.3%
Vomiting	50%	3%	6.3%	0.3%

[a] *Data from Phase I single-agent idasanutlin study NP27872; all patients were dosed for 5 days.*

[b] *Data from rituximab monotherapy.*

5.1.5 Management of Specific Adverse Events

During induction, study treatment may be delayed for toxicity for a maximum of 21 days. If study treatment is delayed for >21 days, obinutuzumab *or rituximab* and idasanutlin treatment will be permanently discontinued (see Table 16, Table 17, and Table 18).

Treatment delays apply to all toxicities described below; dose modifications apply only to toxicities that are considered to be related to idasanutlin. There will be no dose reductions of obinutuzumab *or rituximab.* Idasanutlin dose may be reduced as outlined in Table 16. There will be no more than one dose reduction per treatment cycle. If the idasanutlin dose is reduced, re-escalation is not permitted.

Table 16 Idasanutlin Dose Reduction Steps

Initial Dose	Dose Reduction by (mg)		
	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.

Guidelines for management of toxicities during induction treatment are provided in Section 5.1.5.1. Guidelines for management of toxicities during maintenance treatment are provided in Section 5.1.5.2.

5.1.5.1 Toxicities during Induction Treatment

Hematologic Toxicities

Table 17 provides guidelines for management of hematologic toxicities that occur during induction treatment, with the exception of Days 8 and 15 of Cycle 1. Table 18 provides guidelines for management of hematologic toxicities that occur on Days 8 and 15 of Cycle 1, when patients are to receive treatment with obinutuzumab only. Hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia. Lymphopenia is not considered hematologic toxicity but an expected outcome of therapy.

Table 17 Guidelines for Management of Hematologic Toxicities That Occur during Induction Treatment (Except for 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, two, or no prior dose reductions:** • Withhold study treatment. [a] • Administer RBCs or platelets as required. • If patient has not already initiated G-CSF, initiate prophylactic G-CSF for current and subsequent cycles. • If improvement to Grade • 2 or baseline • 14 days after the scheduled date for the next cycle, resume obinutuzumab *or rituximab* at full dose and resume idasanutlin at current dose. • If improvement to Grade • 2 or baseline 15• 21 days after the scheduled date for the next cycle, resume obinutuzumab *or rituximab* at full dose and resume idasanutlin at a reduced dose according to guidelines in Section 5.1.5 for current and subsequent cycles. • If study treatment is withheld for > 21 days, permanently discontinue study treatment. • Permanently discontinue study treatment if any of the following events occur: Grade 3 or 4 thrombocytopenia *of any duration if associated with Grade ≥ 3 bleeding* Recurrent Grade 3 or 4 neutropenia associated with fever of > 38°C (> 5 days) or a documented infection despite use of G-CSF and after one idasanutlin dose reduction Recurrent Grade 4 neutropenia or thrombocytopenia lasting more than 7 days despite use of G-CSF (for neutropenia) and after one idasanutlin dose reduction **For patients who have had three prior dose reductions** ***or for patients who reach the lowest dose level and no further dose reduction is applicable (see Section 5.1.5)*****:** • Permanently discontinue study treatment.

G-CSF = granulocyte colony-stimulating factor; NHL = non-Hodgkin's lymphoma.

[a] Treatment delays apply to all toxicities; dose modifications apply only to toxicities that are considered to be related to idasanutlin

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

Table 18 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 until resolution of fever and infection (as applicable). • If the event is ongoing on Day 1 of Cycle 2, follow instructions in Table 17. Note: Obinutuzumab should not be withheld for asymptomatic neutropenia.
Severe thrombocytopenia [a] or bleeding	• Withhold obinutuzumab until platelet count • 50,000/• L and resolution of bleeding. • If the event is ongoing at Day 1 of Cycle 2, follow instructions in Table 17.

[a] Severe thrombocytopenia is defined as a platelet count < 10,000/• L for patients who are not receiving concomitant anticoagulants or platelet inhibitors.

Non-Hematologic Toxicities during Induction Treatment

Table 19 provides guidelines for the management of non-hematologic toxicities that occur during induction treatment.

Table 19 Guidelines for Management of Non-Hematologic Toxicities

Event	Action to Be Taken
General guidance for treatment delays and discontinuation	• 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. • If study treatment is withheld for > 21 days because of a toxicity that is attributable to study treatment, permanently discontinue study treatment.
IRRs and anaphylaxis	• Guidelines for the management of IRRs and anaphylaxis are provided in Section 5.1.1.1 and Appendix 9. • In case of Grade 4 IRRs or anaphylaxis, study treatment should be permanently discontinued.
TLS	• Withhold study treatment. [a] • Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. • If symptoms have resolved completely, resume obinutuzumab *or rituximab* and idasanutlin at full dose
New-onset neurologic manifestations suggestive of PML	• Withhold study treatment. [a] • Consult with a neurologist if PML is suspected (refer to Section 5.1.1.5 for guidance on investigations). • If PML is ruled out, resume obinutuzumab *or rituximab* and idasanutlin at full dose. • If PML is confirmed, permanently discontinue study *treatment.*
AST, ALT, or bilirubin increase: Grade • 3 (or • 10 • ULN for patients with liver involvement)	• Withhold study treatment. [a] • If improvement to Grade • 1 *(or ≤ 5 • ULN (Grade 2) for patients with liver involvement)*, resume obinutuzumab *or rituximab* and idasanutlin at full dose for current and subsequent cycles. • Permanently discontinue study treatment for life-threatening liver toxicity *(including Hy's Law cases).*

Table 19 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event	Action to Be Taken
Diarrhea	Grade 4 diarrhea: Permanently discontinue study treatment. Grade 2 or 3 diarrhea: • If Grade 3 diarrhea occurs between Day 1 and Day 5 of the treatment cycle, withhold study treatment only if diarrhea does not improve to Grade • 2 within 48 hours with appropriate treatment. After dose withheld, if diarrhea improved to Grade • 2, resume obinutuzumab *or rituximab* at full dose and resume idasanutlin at a reduced dose according to guidelines in Section 5.1.5 for current and subsequent cycles. • If Grade 3 diarrhea is present at the time of the next planned cycle, withhold study treatment. If diarrhea improved to Grade • 2, resume obinutuzumab *or rituximab* at full dose and resume idasanutlin at a reduced dose according to guidelines in Section 5.1.5 for current and subsequent cycles. Management for diarrhea: • Initiate treatment at the time of onset. • Administer loperamide 4 mg as loading dose; and up to 2 mg every 4 h or after every unformed stool (for a maximum daily dose of 16 mg), or per institutional standard. For subsequent episodes, use 4 mg QD prophylactic loperamide 30 minutes before subsequent dosing. Encourage patients to self-medicate with loperamide 2 mg should diarrhea recur (up to 2 mg every 4 h or after every unformed stool for a maximum daily dose of 16 mg), or per institutional standard. • Monitor electrolyte levels closely and correct as appropriate. • Administer IV fluids as clinically indicated. • Upon presentation of Grade 3 diarrhea, exclude presence of active infections (e.g., *Clostridium difficile*). If present, treat infection(s) according to local guidelines.
Nausea and vomiting	• Administer second-generation anti-emetics like palonosetron, ondansetron, or granisetron. If vomiting occurs within 15 minutes of

Table 19 Guidelines for Management of Non-Hematologic Toxicities (cont.)

Event		Action to Be Taken
		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.
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, nausea, and vomiting	Grade 3 or 4	**For patients who have had no prior dose reductions:** • Withhold study treatment. [a] • If improvement to Grade • 1 or baseline, resume obinutuzumab *or rituximab* at full dose and resume idasanutlin at a reduced dose [a] for current and subsequent cycles according to guidelines in Section 5.1.5 for current and subsequent cycles. **For patients who have had one prior dose reduction:** Grade 4 events • Permanently discontinue study treatment. Grade 3 events Withhold study treatment. [a] • If improvement to Grade • 1 or baseline, resume obinutuzumab *or rituximab* at full dose and idasanutlin at a reduced dose according to guidelines in Section 5.1.5 for current and subsequent cycles. **For patients who have had two prior dose reductions *or for patients who reach the lowest dose level and no further dose reduction is applicable (See Section 5.1.1.5)*:** Permanently discontinue study treatment.
	Grade 2	• Withhold study treatment. [a] • If improvement to Grade • 1 or baseline, resume obinutuzumab *or rituximab* at full dose and idasanutlin at current dose

h = hour; IRR = infusion-related reaction; PML = progressive multifocal leukoencephalopathy; QD = once a day; TLS = tumor lysis syndrome; 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.

5.1.5.2 Toxicities during Maintenance Treatment

Table 20 provides guidelines for management of toxicities that occur during maintenance treatment.

Table 20 Guidelines for Management of Toxicities That Occur during Maintenance Treatment

Event	Action to Be Taken
Hematologic toxicity: Grade 3 or 4	• Withhold *study treatment.* • Administer myeloid growth factors for neutropenia as allowed according to institutional guidelines. • If improvement to Grade • 2, resume obinutuzumab *or rituximab* at full *dose and idasanutlin at reduced* dose. • If *study treatment* is withheld for >42 days, permanently discontinue.
Non-hematologic toxicity: Grade • 2	• Withhold *study treatment* • If improvement to Grade • 1 or baseline, administer obinutuzumab *or rituximab* at full *dose and idasanutlin at reduced* dose. • If *study treatment* is withheld for >42 days, permanently discontinue.

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 drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 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 drug
- 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 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 • 3 neutropenia, including febrile neutropenia
- Grade • 2 diarrhea
- Grade • 3 thrombocytopenia or Grade 2 thrombocytopenia if associated with hemorrhage/bleeding
- *Grade • 2 Clostridium difficile infection*
- *Second malignancies*

5.2.4 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

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

5.2.5 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 (except for TLS).

The following adverse events are considered selected adverse events:

- Thrombocytopenia, including acute thrombocytopenia (events occurring during and within 24 hours following obinutuzumab infusion)
- Hepatitis B reactivation
- Cardiac events

- TLS
- IRRs
- All infections, including PML
- Neutropenia, including prolonged neutropenia (neutropenia $<$1000 cells/• L that does not resolve after 28 days without obinutuzumab treatment) and late-onset neutropenia (neutropenia $<$1000 cells/• L occurring • 28 days after obinutuzumab treatment has been completed or stopped)
- Gastrointestinal 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 study treatment. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment.

An exception is made for Grade 3 or 4 infections (related and unrelated) *in patients who received obinutuzumab,* which should be reported 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).

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 21 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 21 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, considering especially the effects of study treatment modifications or discontinuation of study treatment, 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 gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

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

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

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

5.3.5.8 Deaths

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

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

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Lymphoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should **not** be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the *modified* Lugano 2014 criteria (see Appendix 5). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills 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 over dosage is available from human clinical studies. In clinical studies with obinutuzumab at 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 whose B cells are 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 study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list

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

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)
- Occurrence of DLT

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites:

Medical Monitor: [redacted], M.D., Ph.D.

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 Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor 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 with use of 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 study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form with use of the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within *18* months after the last dose of study treatment *for those receiving obinutuzumab and idasanutlin and within 12 months after the last dose of study treatment for those receiving rituximab and idasanutlin*. 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 with use of 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 with use of 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. Once the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or study-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 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as within 90 days after the last dose of study treatment), if the event is believed to be related to prior study treatment. 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 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 these events 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 with use of 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 should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as within 90 days after last dose of study treatment), if the event is believed to be related to prior study treatment.

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

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

This Phase Ib/II, open-label, multicenter, non-randomized dose-escalation study will evaluate the safety, efficacy, and pharmacokinetics of idasanutlin and obinutuzumab in patients with R/R FL *and of idasanutlin and rituximab in R/R* DLBCL.

Study data will be summarized separately for dose escalation and expansion phase. Data from the dose-escalation phase will be summarized by dose level. Data from the expansion phase will be summarized by histologic subtype (i.e., FL or DLBCL).

6.1 DETERMINATION OF SAMPLE SIZE

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 algorithm, as outlined in Section 3.1. It is anticipated that enrollment of up to eight cohorts of 3• 6 patients each, for a total of 9• 40 patients, will be required to establish the RP2D during the dose-escalation phase (See Appendix 11 for modeling details). The estimated probability to require more than 30 patients in the investigated scenarios in Appendix 11 is generally less than 5%.

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 (GAUDI study/BO21000 and Gadolin/GO01297), and 40% in DLBCL assuming an observed PET-defined CR rate of 55%. Table 22 provides 90% Clopper-Pearson exact CIs for the probability of achieving an EOI PET-defined CR for a range of observed proportions based on a sample of 40 patients.

Table 22 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)

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 PATIENT CHARACTERISTICS

Summaries of patient characteristics will be performed by disease cohort. Enrollment, major protocol violations, and discontinuations from the study will be listed. Demographics as well as the incidence of treatment discontinuation for reasons other than disease progression will be tabulated.

Data related to administration of study treatment components will be listed, and any dose modifications will be flagged. The number of doses, treatment cycles, and the average dose received for each treatment group will be summarized using descriptive statistics (mean, standard deviation, median, and range).

6.3 SAFETY ANALYSES

The major safety objective is to determine the DLT of idasanutlin in combination with obinutuzumab *or rituximab.* Safety will be assessed through summaries of adverse events and changes from baseline laboratory test results, and vital signs. Incidence of clinically significant ECG abnormalities will be reported in patient listings and change from baseline summarized in tables. ECG QT and QTcF intervals will be summarized by descriptive statistics.

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

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

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

The primary safety population will include patients who received at least one dose of *any* component of the combination.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will be performed and will include all patients enrolled in the expansion phase, who received at least *one dose of any component of the combination.* Data from patients *who were dosed at the RP2D with the recommended Phase 2 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 5).

6.4.1 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 EOI. Patients without a post-baseline tumor assessment will be considered non-responders.

6.4.2 Secondary Efficacy Endpoints

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

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

- Best response of CR or PR during the study, as determined by the investigator on the basis of CT scans alone

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.

6.4.3 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 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:

- PFS, defined as the time from initiation of study treatment to first occurrence of disease progression or relapse, as determined by 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 investigator on the basis of CT scans alone, initiation of new anti-lymphoma therapy, or death from any cause, whichever occurs first
- 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
- OS, defined as the time from initiation of study treatment to death from any cause

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 valid tumor assessment, i.e., CR, PR, or SD. For patients without post-baseline tumor assessments, data will be censored at the date of initiation of study treatment plus 1. For the OS analysis, data for patients who have not died will be censored at the date the patient was last known to be alive. Where medians are reached, the corresponding estimated

median will be provided, along with the 95% CI using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). In addition, where available at the time of the analysis, landmark estimates of the proportion of patients who are event free at 6 months, 9 months, 1 year, and 2 years will be provided, along with 95% asymptotic CIs using Greenwood's formula for standard errors.

6.5 PHARMACOKINETIC ANALYSES

Individual and mean serum concentrations of obinutuzumab *or rituximab* and *plasma concentrations of* idasanutlin will be tabulated and plotted *after appropriate grouping*. Summary statistics of concentration data will be computed for each scheduled sampling time for each analyte. Interpatient variability and drug accumulation after multiple doses will be evaluated. Compartmental, non-compartmental, and/or population approaches will be considered as appropriate. Potential drug interactions may be assessed by comparison of pharmacokinetics in the current study with historical data. Potential correlations between PK exposure and demographic and pathophysiological covariates may be explored by population PK analysis. Potential correlations between PK exposure and PD, efficacy, and safety endpoints may be explored by graphical analysis and PK-PD modeling. The assessment of PK parameters and related analyses will be performed per the Sponsor's discretion, taking into consideration the appropriateness of the PK data collected and the study outcome.

6.6 BIOMARKER ANALYSIS

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.

6.7 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 the 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.

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 study.

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 onto 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 study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by

relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of 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 [LPLV]).

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

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

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study 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 Website:

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 studies 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 study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies 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 studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities for Patients with Follicular Lymphoma
(Dose-Escalation and Expansion Phases)

	Screening [a]		Induction (6 Cycles; 28-Day Cycles)								EOI	Maint. (24 Months)	EOM [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
	D –28 to D –1	D –14 to D –1	Cycle 1 (± 1 d)				Cycle 2 (± 2 d)		Cycles 3–6 (± 2 d)		After Last Induction Dose [c]	Every 2 Months (± 1 wk)	35 Days After Last Dose		
			D1	D5	D8	D15	D1	D15	D1	D15		D1			
Informed consent [e]	x														
Demographic data	x														
Medical history	x														
ECOG Performance Status	x														
Vital signs [f]	x		x		x	x	x		x		x [g]	x	x		
Height	x														
Weight and body surface area	x														
12-lead ECG	x		x [h]	x [h]					x [i]		x	*x* [h]	x		
Complete physical examination [j,k]	x														
Targeted physical examination [k,l]			Cycles 2 and 4								x	x	x	x	
Ann Arbor, FLIPI, and FLIPI2	x														
B symptoms [m]	x														
β_2 microglobulin			x												
Hematology [n]		x	x [o,p]		x [p]	x [p]	x [p]	x	x [p]	x	x [g]	x	x		

Appendix 1
Schedule of Activities for Patients with Follicular Lymphoma (Dose-Escalation and Expansion) (cont.)

	Screening [a]		Induction (6 Cycles; 28-Day Cycles)								EOI	Maint. (24 Months)	EOM [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
	D • 28 to D • 1	D • 14 to D • 1	Cycle 1 (± 1 d)				Cycle 2 (± 2 d)		Cycles 3• 6 (± 2 d)		After Last Induction Dose [c]	Every 2 Months (± 1 wk)	35 Days After Last Dose		
			D1	D5	D8	D15	D1	D15	D1	D15		D1			
Serum chemistry [q]		x	x [o, p]		x [p]	x [p]	x [p]	x	x [p]	x	x [g]	x	x		
Coagulation (INR, aPTT [or PTT], and PT)		x													
Pregnancy test [r]		x									x [g]		x		
Hepatitis B and C testing [s]	x														
Quantitative IgA, IgG, IgM			x								x	x [t]	x	x [u]	
PK sample for obinutuzumab			x [v]												
PK sample for idasanutlin			x [v]												
Whole blood for MRD [w]			x [p]				x				x	x [t]	x		
Whole blood for lymphocyte immunophenotyping [x]			x [p]			x [p]	x [p]		x [p]		x	x [t]	x	x [u]	
Serum for MIC-1			x [v]	x [v]			x [v,y]		x [v,z]						
Optional peripheral blood sample for RCR [aa]			x	x											
Tumor tissue specimen (leftover tissue may be used for optional RCR specimen [bb])	x [bb]		x [cc]												

Appendix 1
Schedule of Activities for Patients with Follicular Lymphoma (Dose-Escalation and Expansion) (cont.)

		Screening [a]		Induction (6 Cycles; 28-Day Cycles)								EOI	Maint. (24 Months)	EOM [b]	Post-Treatment FU Period (Q3M) [d]	Survival FU Period (Q3M) [d]
		D • 28 to D • 1	D • 14 to D • 1	Cycle 1 (± 1 d)				Cycle 2 (± 2 d)		Cycles 3• 6 (± 2 d)		After Last Induction Dose [c]	Every 2 Months (± 1 wk)	35 Days After Last Dose		
				D1	D5	D8	D15	D1	D15	D1	D15		D1			
Concomitant medications		x		To be recorded continually until end of treatment												
Adverse events [dd]		x		To be assessed continually [dd]												
PET-CT scan		x [ee]										x [ff]	x [gg]			
CT scan [hh]		x [hh]						x [oo]				x [ff]	x [ii]	x [jj]	x [kk]	
Bone marrow biopsy and aspirate		x [ll]										x [ff,mm]	x [mm]	x [jj,mm]		
Study treatment administration	Obinutuzumab [nn]			x		x	x	x		x			x			
	Idasanutlin [nn]			D1-D5				D1-D5		D1-D5			x [pp]			
New anti-lymphoma treatment															x	x
Survival follow-up																x

CT = computed tomography; D = day; Discont. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOI = end of induction; EOM = end of maintenance; FLIPI = Follicular Lymphoma International Prognostic Index; FU = follow-up; Maint. = maintenance; MRD = minimal residual disease; MIC = macrophage inhibitory cytokine-1; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; Q3M = every 3 months; RCR = Roche Clinical Repository; wk = week.

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

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

Appendix 1
Schedule of Activities for Patients with Follicular Lymphoma (Dose-Escalation and Expansion) (cont.)

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

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

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

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

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

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

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

[h] All ECGs should be collected prior to and 6 hours after idasanutlin administration or after obinutuzumab administration, whichever occurs later. For Cycle 1 Day 5 in the induction phase, perform ECG 6 hours post idasanutlin administration only if patient is still at clinic.

[i] All ECGs should be collected prior to and 6 hours after idasanutlin administration or after obinutuzumab administration, whichever occurs later. ECGs will be performed as described on Cycle 4, Days 1 and 5 only. For Cycle 4 Day 5, perform ECG 6 hours post idasanutlin administration only if patient is still at clinic.

[j] 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.

[k] 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.

[l] 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.

Appendix 1
Schedule of Activities for Patients with Follicular Lymphoma (Dose-Escalation and Expansion) (cont.)

[m] Unexplained fever > 38°C, nightsweats, unexplained weight loss > 10% of body weight over 6 months.

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

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

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

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

[r] All women who are not postmenopausal (• 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 on embryo-fetal development, monthly pregnancy testing is strongly recommended for women of childbearing potential (CTFG 2014).

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

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

[u] 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.

[v] See Appendix 3 and Appendix 4 for detailed schedule.

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

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

[y] Also on Day 5 of this cycle. See Appendix 3 and Appendix 4 for detailed schedule.

[z] Cycle 4 Day 1 and Day 5. See Appendix 3 and Appendix 4 for detailed schedule.

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

[bb] Availability of adequate archival or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.6.2 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 3–4 infections (related and unrelated), 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

Appendix 1
Schedule of Activities for Patients with Follicular Lymphoma (Dose-Escalation and Expansion) (cont.)

is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to any of the study treatment components or trial-related procedures until a final outcome can be reported.

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

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

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

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

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

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

[kk] Perform every 6 months.

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

[mm] For patients with bone marrow involvement at screening, a repeat assessment will be performed at EOI if there is radiologic evidence of a complete response, and during maintenance or at EOM if there is radiologic evidence of a complete response or if clinically indicated (e.g., if there is clinical suspicion of progressive disease in the bone marrow with no radiologic evidence of progression).

[nn] Refer to Section 4.3.2.3 and Section 4.3.2.5 for details on dosing and schedule.

[oo] Perform within 7 days prior to Day 1 of Cycle 3.

[pp] *Regimen will be defined based on available safety, tolerability, PK, and PD data.*

Appendix 2
Schedule of Activities for Patients with DLBCL

	Screening [a]		Induction (6 Cycles; 28-Day Cycles)								EOI		*EOC* [d]		
			Cycle 1 (±1 d)				Cycle 2 (±2 d)		Cycles 3–6 (±2 d)		After Last Induction Dose [b]	*Consolidation (6 months)* [c]	*35 Days after Last Dose*	Post-Treatment FU Period (Q3M) [e]	Survival FU Period (Q3M) [e]
	D −28 to D −1	D −14 to D −1	D1	D5	D8	D15	D1	D15	D1	D15					
Informed consent [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														
12-lead ECG	x		x [j]	x [j]					x [k]		x	*x* [j]	*x*		
Complete physical examination [l,m]	x														
Targeted physical examination [m,n]			Cycles 2 and 4								x	x [i]	*x*	x	
Ann Arbor, IPI	x														
B symptoms [o]	x														
β_2 microglobulin			x												
Hematology [p]		x	x [q,r]		x [r]	x [r]	x [r]	x	x [r]	x	x	*x* [i]	*x*		
Serum chemistry [s]		x	x [q,r]		x [r]	x [r,t]	x [r]	x [t]	x [r]	x [t]	x	*x* [i]	*x*		

Appendix 2
Schedule of Activities for Patients with DLBCL (cont.)

	Screening [a]		Induction (6 Cycles; 28-Day Cycles)								EOI		*EOC* [d]		
	D • 28 to D • 1	D • 14 to D • 1	Cycle 1 (±1 d)				Cycle 2 (±2 d)		Cycles 3• 6 (±2 d)		After Last Induction Dose [b]	*Consolidation (6 months)* [c]	*35 Days after Last Dose*	Post-Treatment FU Period (Q3M) [e]	Survival FU Period (Q3M) [e]
			D1	D5	D8	D15	D1	D15	D1	D15					
Coagulation (INR, aPTT [or PTT], and PT)		x													
Pregnancy test [u]		x									x		*x*		
Hepatitis B and C testing [v]	x														
Quantitative IgA, IgG, IgM			x								x	x [w]	*x*	x [x]	
PK sample for obinutuzumab			x [y]												
PK sample for rituximab			*x* [y]												
PK sample for idasanutlin			x [y]												
Whole blood for MRD [z]			x [r]				x				x	*x* [aa]	*x*		
Whole blood for lymphocyte immunophenotyping [bb]			x [r]			x [r]	x [r]		x [r]		x	x [aa]	x	x [x]	
Serum for MIC-1			x [y]	x [y]			x [y,cc]		x [y,dd]						
Optional peripheral blood sample for RCR [ee]			x	x											
Tumor tissue specimen (leftover tissue may be used for optional RCR specimen [ff])	x [ff]		x [gg]												
Concomitant medications	x		To be recorded continually until end of treatment												
Adverse events [hh]	x		To be assessed continually [hh]												

Appendix 2
Schedule of Activities for Patients with DLBCL (cont.)

		Screening [a]		Induction (6 Cycles; 28-Day Cycles)								EOI		*EOC* [d]		
		D • 28 to D • 1	D • 14 to D • 1	Cycle 1 (±1 d)				Cycle 2 (±2 d)		Cycles 3• 6 (±2 d)		After Last Induction Dose [b]	*Consolidation (6 months)* [c]	*35 Days after Last Dose*	Post-Treatment FU Period (Q3M) [e]	Survival FU Period (Q3M) [e]
				D1	D5	D8	D15	D1	D15	D1	D15					
PET-CT scan		x [ii]										x [jj]		x [jj]		
CT scan [kk]		x [kk]						x [ll]				x [jj]	x [mm]	x [jj]	x [nn]	
Bone marrow biopsy and aspirate		x [oo]										x [jj,pp]	x [pp]	x [jj,qq]		
Study treatment administration	Obinutuzumab [rr]			x		x	x	x		x						
	Rituximab [rr]			*x*				*x*		*x*			*x*			
	Idasanutlin [rr]			D1• D5				D1• D5		D1• D5			*x* [ss]			
New anti-lymphoma treatment															x	x
Survival follow-up																x

CT = computed tomography; D = day; Discont. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; *EOC = end of consolidation;* EOI = end of induction; FU = follow-up; IPI = International Prognostic Index; MRD = minimal residual disease; MIC= macrophage inhibitory cytokine-1; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; Q3M = every 3 months; RCR = Roche Clinical Repository; wk = week.

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

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

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

[b] EOI will be treatment completion visit. 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.

Appendix 2
Schedule of Activities for Patients with DLBCL (cont.)

[c] *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 8 months.*

[d] *Patients who complete consolidation treatment or discontinue consolidation treatment prematurely will undergo assessments at the EOC.*

[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. Patients who experience disease progression will undergo limited assessments every 3 months during the survival FU period, which will continue until the end of the study. The end of the study is defined as the time when all enrolled patients with FL have completed or discontinued study treatment and all enrolled patients with DLBCL 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 in patients who had experienced an infusion-related reaction during a prior infusion.

[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. For rituximab infusions: Vital signs monitoring during infusion should be determined as per local label.*

[j] All ECGs should be collected prior to and 6 hours after idasanutlin administration or after obinutuzumab/*rituximab* administration, whichever occurs later. For Cycle 1 Day 5, perform ECG 6 hours post idasanutlin administration only if patient is still at clinic.

[k] All ECGs should be collected prior to and 6 hours after idasanutlin administration or after obinutuzumab/*rituximab* administration, whichever occurs later. ECG will be performed as described on Cycles 4, Days 1 and 5 only. For Cycle 4 Day 5, perform ECG 6 hours post idasanutlin administration only if patient is still at clinic.

[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.

Appendix 2
Schedule of Activities for Patients with DLBCL (cont.)

[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, nightsweats, 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 72 hours prior to Day 1 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 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] *Only patients treated with obinutuzumab.*

[u] All women who are not postmenopausal (• 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days prior to Day 1 of Cycle 1. Because of the suspected effect of idasanutlin on embryo-fetal development, monthly pregnancy testing is strongly recommended for women of childbearing potential (CTFG 2014).

[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 4 months after initiation of consolidation treatment.*

[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] See Appendix 3 for detailed schedule.

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

[aa] *Perform at the same time as tumor assessments at 4 months after initiation of consolidation treatment.*

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

[cc] Also on Day 5 of this cycle. See Appendix 3 for detailed schedule.

[dd] Cycle 4 Day 1 and Day 5. See Appendix 3 for detailed schedule.

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

[ff] Availability of adequate archival or freshly biopsied tumor tissue samples should be confirmed at screening (see Section 4.5.6.2 for details).

[gg] A tumor biopsy sample is preferred and recommended at the time of progression unless no adequate tumor site is accessible.

[hh] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until *90* days after the last dose of study

treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment (see Section 5.6). An exception is made for Grade 3–4 infections (related and unrelated) *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.

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

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

[kk] 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.

[ll] *Perform within 7 days prior to Day 1 of Cycle 3.*

[mm] *Perform 4 months after initiation of consolidation treatment.*

[nn] Perform a CT scan 3 and 6 months after EOI visit, and every 6 months thereafter.

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

[pp] 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.*

[qq] *For patients with bone marrow involvement at screening, a repeat assessment will be performed at EOI if there is radiologic evidence of a complete response.*

[rr] Refer to Section 4.3.2.3 and Section 4.3.2.5 for details on dosing and schedule.

[ss] *Regimen will be defined based on available safety, tolerability, PK, and PD data.*

Appendix 3
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab *or Rituximab* and Idasanutlin *in Regimen A*

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	*Serum Rituximab Pharmacokinetic Sample* [a]	Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample [b]
Dose-Escalation Phase (Induction Treatment) (28-Day Cycles)				
Cycle 1	Day 1 [c]	Pre-infusion *any time prior the first dose that day*; 30 (±10) minutes after end of infusion	*Pre-infusion any time prior the first dose that day; 30 (±10) minutes after end of infusion*	*Pre-administration any time prior the first dose that day* *6 hr (±20 min) post idasanutlin administration*
	Day 5	—		Prior to idasanutlin administration *(within 1 hr prior to dose)* 2 hours *(±10 min)* post-idasanutlin administration 4 hours *(±10 min)* post-idasanutlin administration 6 hours *(±20 min)* post-idasanutlin administration
Cycle 2	Day 1	Pre-infusion *(within 5 hr prior to dose)*; 30 (±10) minutes after end of obinutuzumab infusion	*Pre-infusion (within 5 hr prior to dose)*	*Pre-administration (within 1 hr prior to dose)* *6 hr (±20 min) post idasanutlin administration*
	Day 5	—		(If patient is in clinic) *Pre-administration (within 1 hr prior to dose)* 6 hours *(±20 min)* post-idasanutlin administration

Appendix 3
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab *or Rituximab* and Idasanutlin *in Regimen A (cont.)*

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	*Serum Rituximab Pharmacokinetic Sample* [a]	Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample [b]
Dose-Escalation Phase (Induction Treatment) (28-Day Cycles)				
Cycle 4	Day 1	Pre-infusion *(within 5 hr prior to dose)*; 30 (±10) minutes after end of obinutuzumab infusion	*Pre-infusion (within 5 hr prior to dose)*	*Pre-administration (within 1 hr prior to dose) 6 hours (±20 min) post-idasanutlin administration*
	Day 5	—		(If patient is in clinic) *Pre-administration (within 1 hr prior to dose) 6 hours (±20 min) post-idasanutlin administration*
Cycle 6	Day 1	Pre-infusion *(within 5 hr prior to dose);* 30 (±10) minutes after end of obinutuzumab infusion	*Pre-infusion (within 5 hr prior to dose); 30 (±10) minutes after end of obinutuzumab infusion*	—

Appendix 3
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab *or Rituximab* and Idasanutlin *in Regimen A (cont.)*

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	*Serum or Rituximab Pharmacokinetic Sample* [a]	Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample [b]
Expansion Phase (Induction Treatment; 28-Day Cycles)				
Cycle 1	Day 1 [c]	Pre-infusion *any time prior the first dose that day*; 30 (±10) minutes after end of infusion [d]	*Pre-infusion any time prior the first dose that day; 30 (±10) minutes after end of infusion* [c]	*Pre-administration any time prior the first dose that day* *6 hr (±20 min) post idasanutlin administration*
	Day 5			Prior to idasanutlin administration *(within 1 hr prior to dose)* 2 hours *(±10 min)* post-idasanutlin administration 4 hours *(±10 min)* post-idasanutlin administration 6 hours *(±20 min)* post-idasanutlin administration
Cycle 2	Day 1	Pre-infusion *(within 5 hr prior to dose)*; 30 (±10) minutes after end of obinutuzumab infusion	*Pre-infusion (within 5 hr prior to dose)*	*Pre-administration (within 1 hr prior to dose)* *6 hr (±20 min) post idasanutlin administration*
	Day 5			(If patient is in clinic) Prior to idasanutlin administration *(within 1 hr prior to dose)* 6 hours *(±20 min)* post-idasanutlin administration

Appendix 3
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab *or Rituximab* and Idasanutlin *in Regimen A (cont.)*

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	*Serum or Rituximab Pharmacokinetic Sample* [a]	Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample [b]
Expansion Phase (Induction Treatment; 28-Day Cycles)				
Cycle 4	Day 1	Pre-infusion *(within 5 hr prior to dose)*; 30 (±10) minutes after end of obinutuzumab infusion	*Pre-infusion (within 5 hr prior to dose)*	*Pre-administration (within 1 hr prior to dose)* *6 hr (±20 min) post idasanutlin administration*
	Day 5			(If patient is in clinic) Prior to idasanutlin administration *(within 1 hr prior to dose)* 6 hours *(±20 min)* post-idasanutlin administration
Cycle 6	Day 1	Pre-infusion *(within 5 hr prior to dose);* 30 (±10) minutes after end of obinutuzumab infusion	*Pre-infusion (within 5 hr prior to dose); 30 (±10) minutes after end of obinutuzumab infusion*	

Appendix 3
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab *or Rituximab* and Idasanutlin *in Regimen A (cont.)*

Study Visit		Serum Obinutuzumab Pharmacokinetic Sample [a]	Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample [b]
Maintenance Phase (Eligible follicular lymphoma patients from both the escalation and expansion phase)			
Month 1	Day 1	Pre-obinutuzumab infusion *(within 5 hr prior to dose)*	
Month 7	Day 1	Pre-obinutuzumab infusion *(within 5 hr prior to dose)*	
Month 13	Day 1	Pre-obinutuzumab infusion *(within 5 hr prior to dose)*	
Month 19	Day 1	Pre-obinutuzumab infusion *(within 5 hr prior to dose)*	
Post-treatment			
Treatment discontinuation		Anytime during visit	
120 days after the last dose		Anytime during visit	
1–2 years after the last dose		Anytime during visit (if patient is in the clinic)	

Appendix 3
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab *or Rituximab* and Idasanutlin *in Regimen A (cont.)*

Study Visit	Serum Obinutuzumab Pharmacokinetic Sample a	Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample b
Maintenance Phase (Eligible follicular lymphoma patients from both the escalation and expansion phase)		
Study Visit	*Serum Rituximab Pharmacokinetic Sample [a]*	*Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample [b]*
Post-treatment		
Treatment discontinuation	*Anytime during visit*	
120 days after the last dose	*Anytime during visit*	
1–2 years after the last dose	*Anytime during visit (if patient is in the clinic)*	

ADA = anti-drug antibody; HACA = human anti–chimeric antibody; HAHA = human anti-human antibody; PK = pharmacokinetic.

[a] *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.*

[b] *Two tubes for plasma and serum, respectively, at each sampling timepoint.*

[c] *The Cycle 1 Day 1 pre-dose PK sample may be taken any time prior to the first dose that day.*

[d] *If the Cycle 1 Day 1 dose of obinutuzumab or rituximab is split over two 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.*

Appendix 4
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab and Idasanutlin in Regimen B

Study Visit		*Serum Obinutuzumab Pharmacokinetic Sample* [a]	*Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample* [b]
Dose-Escalation Phase (Induction Treatment) (28-Day Cycles)			
Cycle 1	*Day 1* [c]	*Pre-obinutuzumab infusion any time prior the first dose that day; 30 (±10) minutes after end of obinutuzumab infusion*	*Pre-administration any time prior obinutuzumab dose that day*
	Day 5		
Cycle 2	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose); 30 (±10) minutes after end of obinutuzumab infusion*	*Pre-administration any time prior the first dose that day* *6 hr (±20 min) post idasanutlin administration*
	Day 5		*Prior to idasanutlin administration (within 1 hr prior to dose)* *2 hours (±10 min) post-idasanutlin administration* *4 hours (±10 min) post-idasanutlin administration* *6 hours (±20 min) post-idasanutlin administration*
Cycle 4	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose); 30 (±10) minutes after end of obinutuzumab infusion*	*Pre-administration (within 1 hr prior to dose)* *6 hours (± 20 min) post-idasanutlin administration*
	Day 5		*(If patient is in clinic)* *Pre-administration (within 1 hr prior to dose)* *6 hours (± 20 min) post-idasanutlin administration*
Cycle 6	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose); 30 (±10) minutes after end of obinutuzumab infusion*	

Appendix 4
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab and Idasanutlin in Regimen B (cont.)

Study Visit		*Serum Obinutuzumab Pharmacokinetic Sample* [a]	*Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample* [b],
Expansion Phase (Induction Treatment; 28-Day Cycles)			
Cycle 1	*Day 1* [c]	*Pre-obinutuzumab infusion any time prior the first dose that day; 30 (±10) minutes after end of obinutuzumab infusion* [d]	*Pre-administration any time prior obinutuzumab dose that day*
	Day 5		
Cycle 2	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose); 30 (±10) minutes after end of obinutuzumab infusion*	*Pre-administration any time prior the first dose that day* *6 hr (±20 min) post idasanutlin administration*
	Day 5		*Prior to idasanutlin administration (within 1 hr prior to dose)* *2 hours (±10 min) post-idasanutlin administration* *4 hours (±10 min) post-idasanutlin administration* *6 hours (±20 min) post-idasanutlin administration*
Cycle 4	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose); 30 (±10) minutes after end of obinutuzumab infusion*	*Pre-administration (within 1 hr prior to dose)* *6 hr (±20 min) post idasanutlin administration*
	Day 5		*(If patient is in clinic)* *Prior to idasanutlin administration (within 1 hr prior to dose)* *6 hours (±20 min) post-idasanutlin administration*
Cycle 6	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose); 30 (±10) minutes after end of obinutuzumab infusion*	

Appendix 4
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab and Idasanutlin in Regimen B (cont.)

Study Visit		*Serum Obinutuzumab Pharmacokinetic Sample* [a]	*Plasma Idasanutlin Pharmacokinetic/Serum MIC-1 Sample* [b]
Maintenance Phase (Eligible follicular lymphoma patients from both the escalation and expansion phase)			
Month 1	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose)*	
Month 7	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose)*	
Month 13	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose)*	
Month 19	*Day 1*	*Pre-obinutuzumab infusion (within 5 hr prior to dose)*	
Post-treatment			
Treatment discontinuation		*Anytime during visit*	
120 days after the last dose		*Anytime during visit*	
1–2 years after the last dose		*Anytime during visit (if patient is in the clinic)*	

Appendix 4
Schedule of Pharmacokinetic and Pharmacodynamic (MIC-1) Assessments for Obinutuzumab and Idasanutlin in Regimen B (cont.)

ADA = anti-drug antibody; PK = pharmacokinetic; HAHA = human anti-human antibody; MIC-1 = macrophage inhibitory cytokine 1.

[a] *Samples collected for PK analysis may be used for additional PK, HAHA, and/or ADA assay development and validation, and additional immunogenicity characterization, at the discretion of the clinical pharmacologist and/or the clinical scientist.*

[b] *Two tubes for plasma and serum, respectively, at each sampling timepoint.*

[c] *The Cycle 1 Day 1 pre-dose PK sample may be taken any time prior to the first dose that day.*

[d] *If the Cycle 1 Day 1 dose of obinutuzumab is split over two 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.*

Appendix 5
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

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

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

Appendix 5
Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (cont.)

Revised Criteria for Response Assessment		
Response and Site	PET-CT–Based Response	CT-Based Response
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5 [b] with reduced uptake compared with baseline and residual mass(es) of any size	• 50% decrease in SPD of up to 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 5
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 5
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: LDi > 1.5 cm and Increase by • 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions • 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation); if uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Appendix 5
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 studies 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 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured; dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

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

Appendix 6
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 7
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 8
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 • 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; LDH = lactate dehydrogenase; 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 8
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
• 2 microglobulin > 1 • 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; LDH = lactate dehydrogenase; 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 8
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 • ULN	
ECOG Performance Status • 2	
Extranodal involvement • 2	
IPI Risk Group	**Number of IPI Risk Factors**
Low	0 or 1
Low-Intermediate	2
High-Intermediate	3
High	4 or 5

ECOG = Eastern Cooperative Oncology Group; FDG = fluorodeoxyglucose; IPI = International Prognostic Index; LDH = lactate dehydrogenase; 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 9
Anaphylaxis Precautions

Equipment Needed

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous (IV), and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

Procedures

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

- Stop the study treatment infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer glucocorticoids, antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 10
Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine clearance (men)} = \frac{(140 - \text{Age}) \cdot \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \cdot 72}$$

$$\text{Creatinine clearance (women)} = \frac{0.85 \cdot (140 - \text{Age}) \cdot \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \cdot 72}$$

Appendix 11
Simulations among the Statistical Design of mCRM

The design shown in Section 3.1.2.3 is investigated here under simulations (of 500 studies) characterized by the following scenario of true toxicities (i.e., the patient data is simulated among the hypothetical true-toxicity), additional scenarios are also investigated as per below:

1. True toxicities equal to the skeleton of prior guesses (Section 3.1.2.3)
2. True toxicities are 30% higher than skeleton of prior guesses
3. True toxicities are 30% lower than skeleton of prior guesses
4. True toxicities are 80% higher than skeleton of prior guesses
5. True toxicities increases stepper at the tail of initial skeleton. This corresponds to Table 1
6. True toxicities are 80% lower than skeleton of prior guesses
7. Based on scenario 1 above it assumed a correlation of 0.5 in the covariance matrix.

Over Scenarios 1• 6, the prior model remains identical to the one evaluated in the body of the document, which is based on historical clinical data, while Scenario 7 investigates the impact of additional correlation in the covariance of prior model. In this Scenario 7, the parameter $\hat{I} \pm$ is then correlated with the parameter $\hat{I}^2$ of the model expressed in the body of the document. Those various dose-toxicity scenarios have been investigated in order to cover a wide range of dose-toxicity possibilities and to be able to quantify the risk and benefit should these scenarios actually occur.

Table 1 Details of Scenario 5

Dose	50	100	150	200	250	300	350	400	450	500	550	600	650	700	750	800
Prior Guess of Risk (%)	3	8	15	22	30	40	45	50	55	60	65	70	75	80	90	100

In Table 2 it is seen that the design under Scenario 1 selected a dose with true risk of toxicity within 25%• 35%, approximately 48% of the time (so above the specified 40%). In addition, this selection is done with help of 38% of patients over 500 simulated studies. It is also noticeable that the percentage of patients in excessive toxicity range (or unacceptable toxicity) remains below the specified 35% (i.e., 24%). Scenario 2 and Scenario 4 represent cases where the true toxicity is a lot higher than expected. This explains the relatively high proportion of patients being in the excessive or unacceptable dose range; however, it is seen in Table 3 that the maximum doses tested are 300 mg and 400 mg, respectively, which is acceptable from a clinical perspective. Scenarios 3 and 6 have true toxicities lower than expected (30% and 80% lower, respectively), as it could be seen in the relative low proportion of patients being in the excessive or unacceptable toxicity. In addition, the dose recommended for Scenario 6 is the

maximum dose tested (i.e., 800 mg), which is unexpected from a clinical perspective. This dose is recommended with the help of a maximum of 45 patients as seen in Table 3.

Table 2 Probability of Dose-Limiting Toxicities under Various Scenarios

		Probability of DLT Obtained over Simulations of 500 Studies		
Scenario/True Toxicity	%	Under-Dosing (0, 0.25)	Targeted Toxicity (0.25, 0.35)	Excessive Toxicity (0.35, 1)
1/Prior guess	Experimentation	37%	38%	24%
	Recommendation	16%	48%	35%
2/30% higher than prior guess	Experimentation	32%	17%	50%
	Recommendation	12%	24%	63%
3/30% lower than prior guess	Experimentation	65%	31%	2.9%
	Recommendation	46%	49%	3.8%
4/80% higher than prior guess	Experimentation	26%	14%	59%
	Recommendation	9.8%	23%	67%
5/toxicity increase on the tail of prior guess	Experimentation	39%	39%	21%
	Recommendation	18%	52%	29%
6/80% lower than prior guess	Experimentation	100%	0%	0%
	Recommendation	100%	0%	0%
7/correlation of 0.5 in the covariance matrix	Experimentation	51%	30%	18%
	Recommendation	29%	45%	25%

In Table 3 it is seen that the design under Scenario 1 (selected design) recommends a dose with a sample size within 9• 24 patients over the 500 simulated studies. In addition, it is noticeable that under a toxicity corresponding to 30% lower than expected toxicity, the sample size remains below 40 patients and below 45 patients for a toxicity 80%.

Appendix 11
Simulations among the Statistical Design of mCRM (cont.)

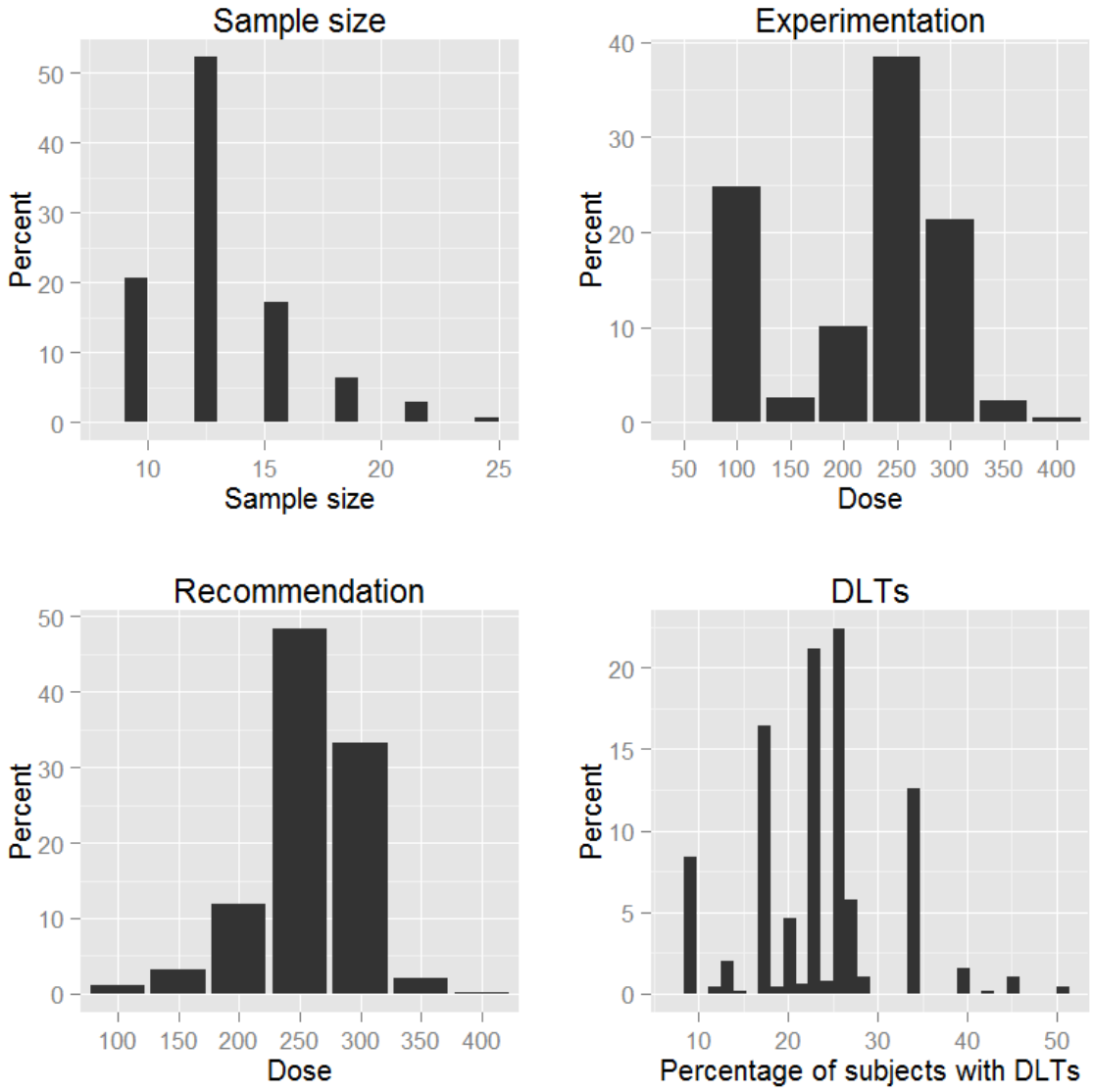
Table 3 Operating Characteristics of the Design under Various Scenarios

Scenario/True Toxicity	True MTD (Simulated)	Maximum Dose Tested *	Selected Dose*	Recommendation of Selected Dose * (%)	Sample Size* [min, n, max]
1/Prior guess	250 mg	400 mg	250 mg	48%	[9, 13, 24]
2/30% higher than prior guess	200 mg	400 mg	250 mg	49%	[9, 13, 24]
3/30% lower than prior guess	350 mg	750 mg	30 0mg	44%	[9, 14, 39]
4/80% higher than prior guess	150 mg	350 mg	200 mg	33%	[9, 15, 27]
5/toxicity increase on the tail of prior guess	250 mg	650 mg	250 mg	52%	[9, 13, 30]
6/80% lower than prior guess	>800 mg	800 mg	800 mg	33%	[12, 30, 45]
7/correlation of 0.5 in the covariance matrix	250 mg	500 mg	250 mg	45%	[9, 15, 33]

* Over 500 simulated studies.

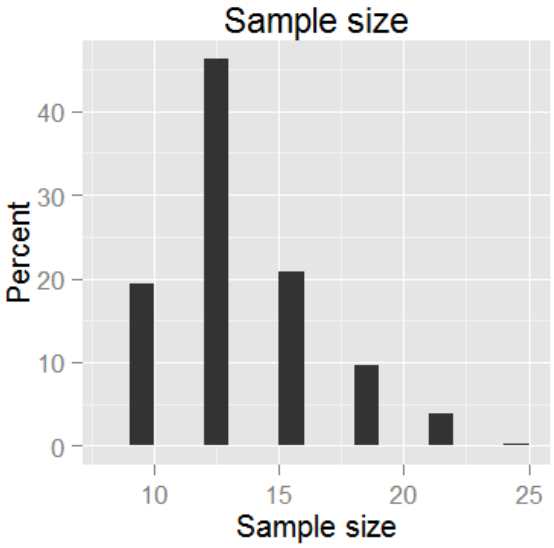
Appendix 11
Simulations among the Statistical Design of mCRM (cont.)

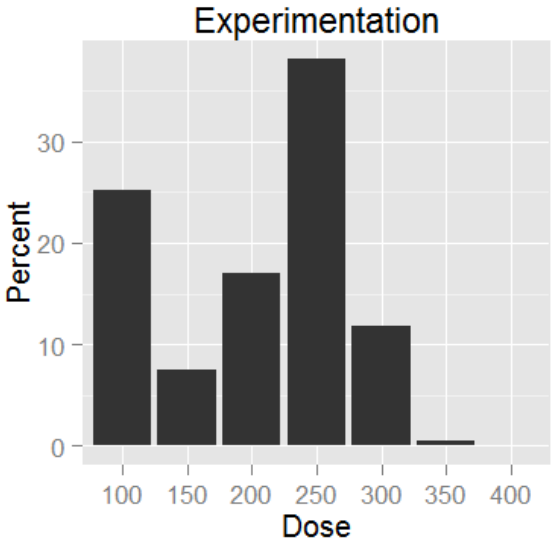
Scenario 1: True Toxicity Matches Prior Guesses

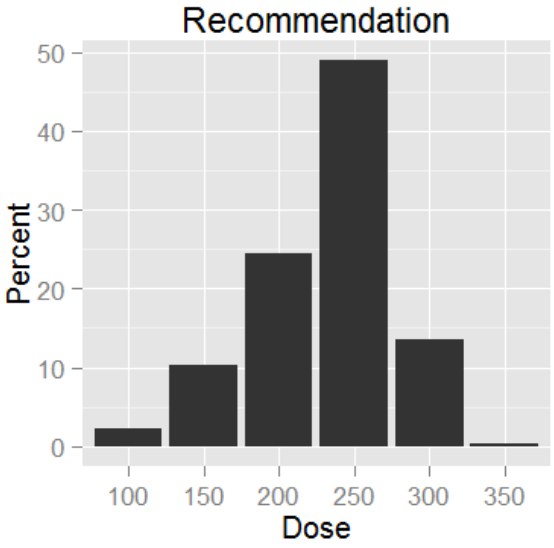


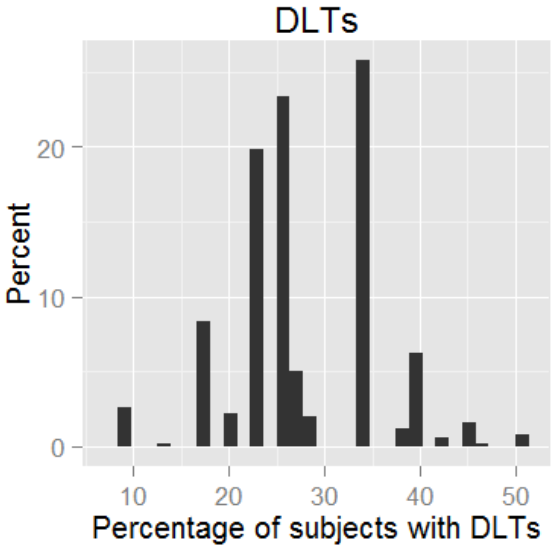
Appendix 11
Simulations among the Statistical Design of mCRM (cont.)

Scenario 2: True Toxicity Is 30% Higher



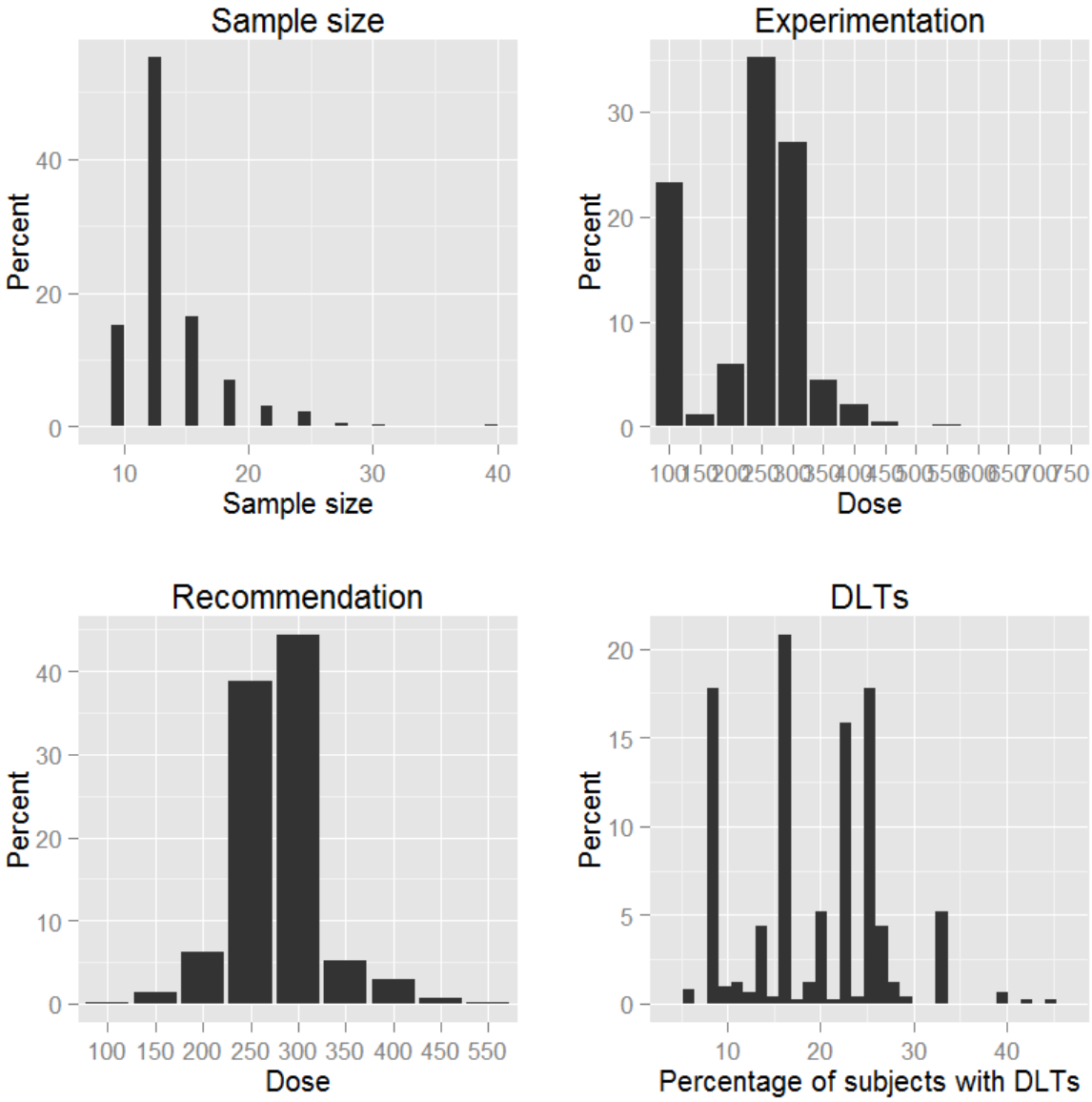






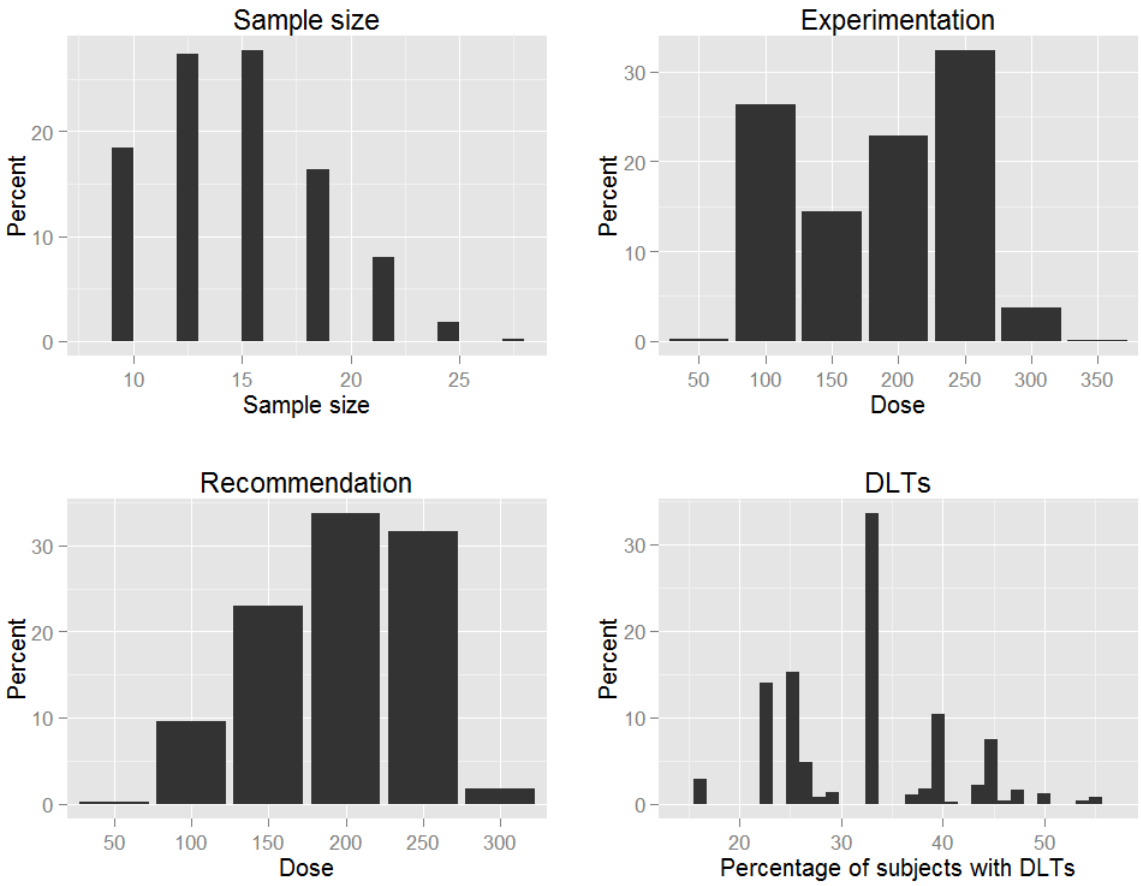
Appendix 11
Simulations among the Statistical Design of mCRM (cont.)

Scenario 3: True Toxicity Is 30% Lower



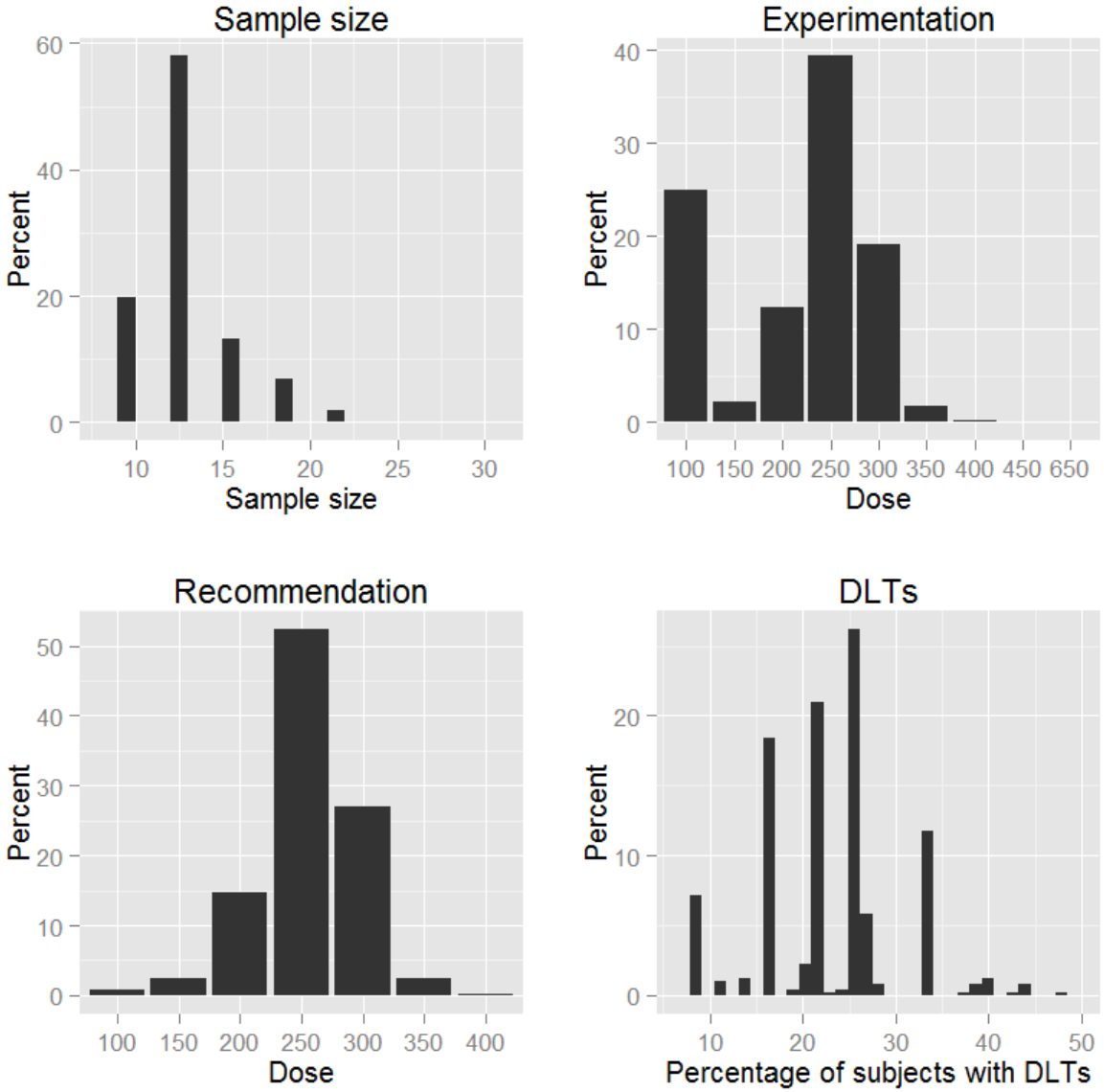
Appendix 11
Simulations among the Statistical Design of mCRM (cont.)

Scenario 4: True Toxicity Is 80% Higher



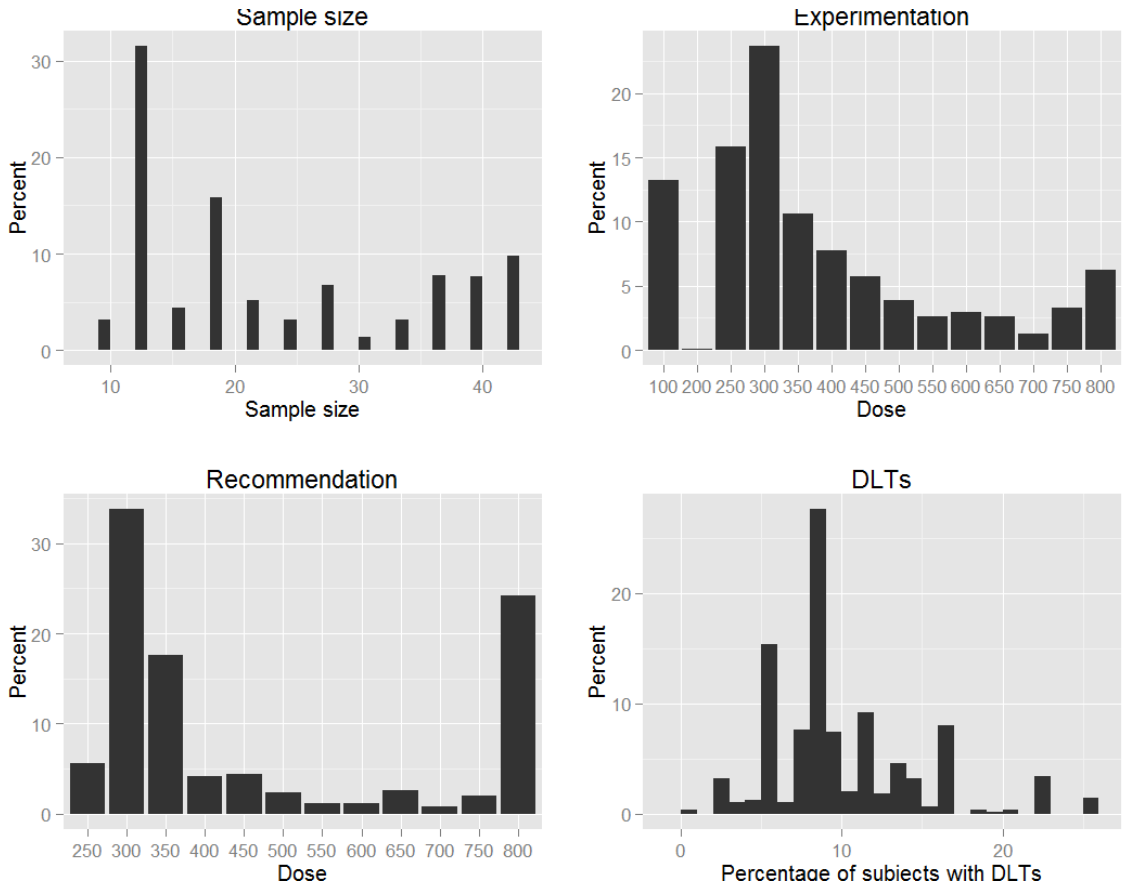
Appendix 11
Simulations among the Statistical Design of mCRM (cont.)

Scenario 5: Steeper Increase on the Tail



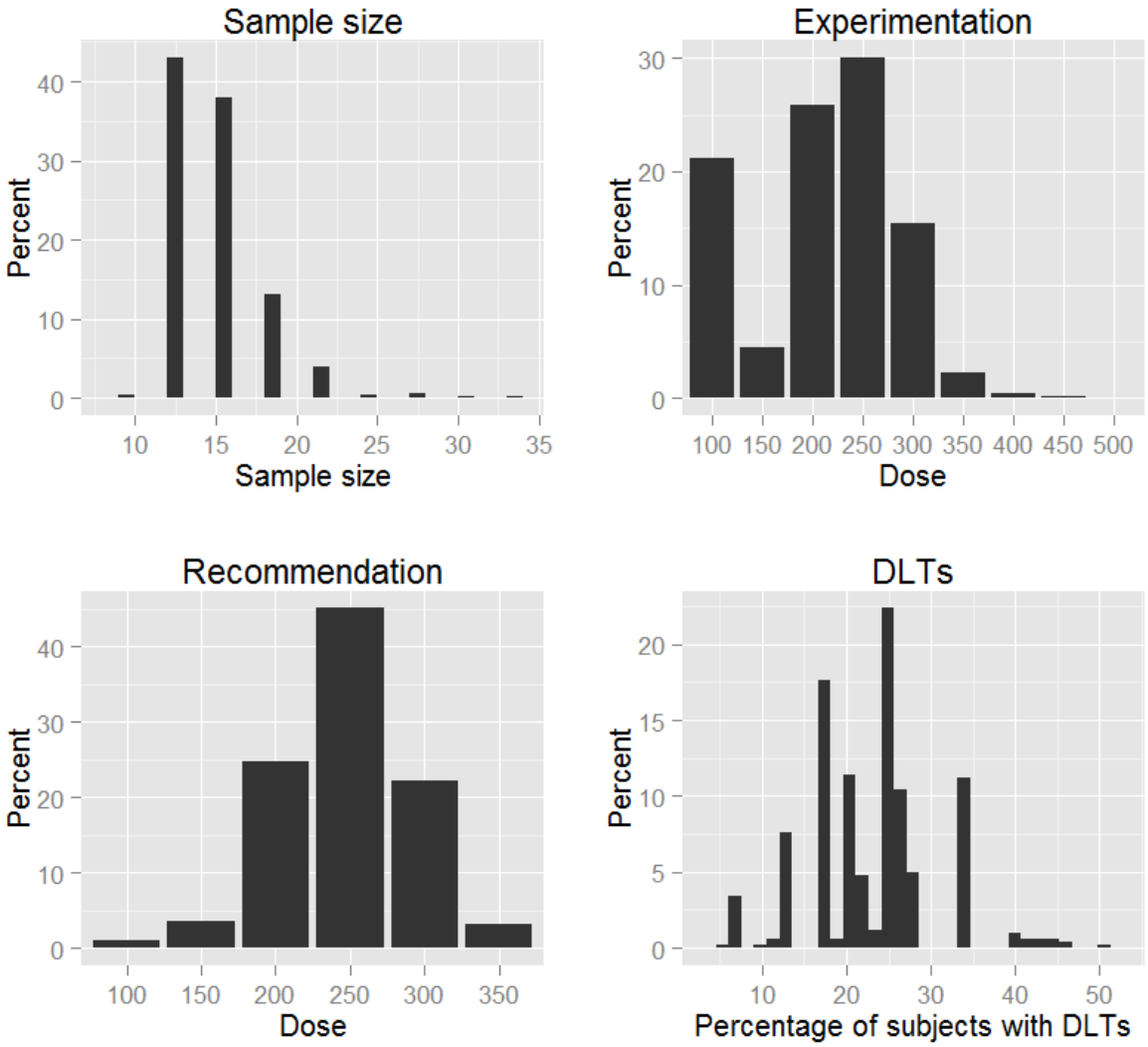
Appendix 11
Simulations among the Statistical Design of mCRM (cont.)

Scenario 6: True Toxicity is 80% Lower than Prior Guesses



Appendix 11
Simulations among the Statistical Design of mCRM (cont.)

Scenario 7: Prior model does include a correlation between



Appendix 12
Safety Overview in Solid Tumor Study NP27872, Including 3 Patients with NHL

Adverse Event	Idasanutlin MBP 100mg QD to1600 BID Weekly (n = 48), n (%)	Idasanutlin MBP 500mg BID to 800 BID Daily • 3 (n = 48), n (%)	Idasanutlin MBP 100mg 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; 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.

Appendix 13
Overall Adverse Events Profile in Patients with Relapsed/Refractory AML• Study NP28679

	n (%)			
	Part 2 Extension		Part 4	
	Idasanutlin (MBP) 600 mg BID N = 17	Idasanutlin (MBP) 600 mg BID plus Cytarabine N = 21	Idasanutlin (SDP) 300 mg BID plus Cytarabine N = 7	Idasanutlin (SDP) 400 mg BID plus Cytarabine N = 8
Total No. of Pts with at Least One AE	17 (100)	21 (100)	7 (100)	8 (100)
Total No. of Events	179	337	95	135
Total No. of Deaths	0	5 (23.8)	0	3 (37.5)
Total No. of Pts Withdrawn due to an AE	1 (5.9)	6 (28.6)	0	2 (25.0)
Total No. of Pts with at Least One				
AE with Fatal Outcome	0	4 (19.0)	0	2 [a] (25.0)
Serious AE	5 (29.4)	13 (61.9)	4 (57.1)	6 (75.0)
Serious AE Leading to Withdrawal	0	6 (28.6)	3 (37.5)	3 (20.0)
Serious AE Leading to Dose Mod/Inter	1 (5.9)	1 (4.8)	1 (14.3)	1 (12.5)
Related Serious AE	1 (5.9)	6 (28.6)	2 (28.6)	3 (37.5)
AE Leading to Withdrawal	1 (5.9)	6 (28.6)	0	3 (37.5)
AE Leading to Dose Mod/Inter	1 (5.9)	3 (14.3)	1 (14.3)	1 (12.5)
Related AE	13 (76.5)	17 (81.0)	6 (85.7)	7 (87.5)
Related AE Leading to Withdrawal	0	4 (19.0)	0	2 (25.0)
Related AE Leading to Dose Mod/Inter	0	1 (4.8)	1 (14.3)	1 (12.5)

AE = adverse event; Inter = interruption; BID = twice daily; MBP = microprecipitated bulk powder; Mod = modification; No. = number; Pts = patients; SDP = spray-dried powder. Note: Related AE = Relationship to idasanutlin is either "remote," "possible," or "probable."

[a] 1 patient died due to an AE of neutropenic sepsis; 1 patient died due to an AE of sepsis.

Source: Appendix 15NP28679_t_ae_profile_ALLPARTSP2E_SE.