CLINICAL RESEARCH PROTOCOL

Protocol Title:	An International, Phase 2, Open-Label, Randomized Study of BGB-3111 Combined with Obinutuzumab Compared With Obinutuzumab Monotherapy in Relapsed/Refractory Follicular Lymphoma
Protocol Identifier:	BGB-3111-212
Phase:	2
Investigational Product:	Zanubrutinib (BGB-3111)
Indication:	Follicular Lymphoma
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Dr. 3rd Floor San Mateo, CA 94404 USA
Reference Numbers:	United States IND 125326 EudraCT 2017-001552-54
Sponsor Medical Monitor	[redacted], MD, PhD Telephone: [redacted] Email: [redacted]
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FINAL PROTOCOL APPROVAL SHEET

An International, Phase 2, Open-Label, Randomized Study of BGB-3111 Combined with Obinutuzumab Compared With Obinutuzumab Monotherapy in Relapsed/Refractory Follicular Lymphoma

BeiGene, Ltd. Approval:

[redacted] MD, PhD	Date
Associate Medical Director	

SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Product: zanubrutinib (BGB-3111)

Title of Study: An International, Phase 2, Open-Label, Randomized Study of BGB-3111 Combined with Obinutuzumab Compared With Obinutuzumab Monotherapy in Relapsed/Refractory Follicular Lymphoma

Protocol Identifier: BGB-3111-212

Phase of Development: 2

Number of Patients: Approximately 210

Study Centers: Approximately 100 sites

Study Objectives:

All primary and secondary objectives will compare zanubrutinib (BGB-3111) plus obinutuzumab versus obinutuzumab monotherapy.

Primary:

- To evaluate efficacy, as measured by overall response rate determined by independent central review

Secondary:

- To evaluate efficacy, as measured by the following:
  - Overall response rate determined by investigator assessment
  - Duration of response determined by independent central review and by investigator assessment
  - Progression-free survival determined by independent central review and by investigator assessment
  - Overall survival
  - Rate of complete response or complete metabolic response determined by independent central review and by investigator assessment
  - Time to response determined by independent central review and by investigator assessment
  - Patient-reported outcomes
- Safety and tolerability
- Pharmacokinetics (zanubrutinib plus obinutuzumab arm only)

Exploratory:

- Overall response rate in obinutuzumab arm after crossover to receive zanubrutinib plus obinutuzumab

Study Design:

This is an international (approximately 100 sites), phase 2, open-label, randomized, active-control study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in 210 patients with relapsed or refractory follicular lymphoma. The primary efficacy endpoint is overall response rate (ORR) determined by independent central review. Disease response will be assessed per the Lugano Classification for Non-Hodgkin Lymphoma (NHL) (Cheson et al, 2014) — hereafter referred to as Lugano Classification for NHL.

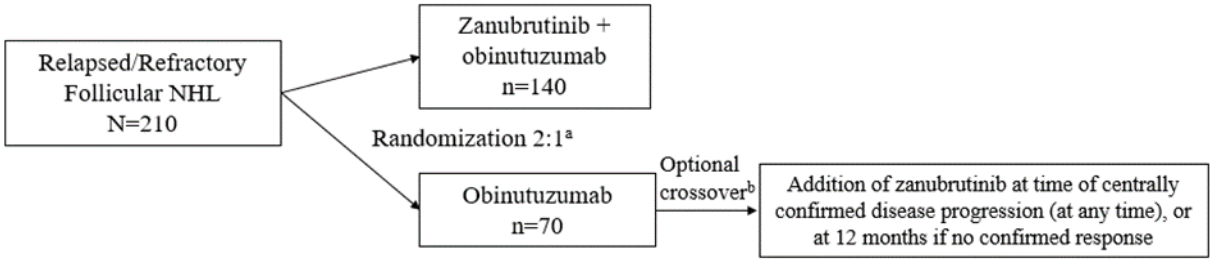
Central randomization (2:1) will be used to assign patients to one of the following study drug treatments:

Arm A: zanubrutinib plus obinutuzumab

Arm B: obinutuzumab monotherapy

Randomization will be stratified by the number of prior lines of therapy (2 to 3 versus > 3), rituximab-refractory status (yes vs no), and geographic region (China vs ex-China). Treatment with zanubrutinib plus obinutuzumab and treatment with obinutuzumab monotherapy will be open label. Study treatment must commence within 5 days after randomization.

Study Schema



Abbreviation: NHL, non-Hodgkin lymphoma.

[a] Randomization stratified by the number of prior lines of therapy (2 to 3 vs > 3), rituximab-refractory status (yes vs no), and geographic region (China vs ex-China).

[b] Option for addition of zanubrutinib following independent central confirmation of disease response status.

Each cycle consists of 28 days. Study drug treatments will be administered as follows, depending on cohort and treatment assignment:

Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food.

Obinutuzumab will be administered 1,000 mg intravenously on days 1, 8, and 15 of Cycle 1, then 1,000 mg on Day 1 of Cycles 2 to 6, then 1,000 mg every 8 weeks. (At the discretion of the investigator, obinutuzumab may be administered 100 mg on Day 1 and 900 mg on Day 2 of Cycle 1 instead of 1,000 mg on Day 1 of Cycle 1.) Responding patients may continue to receive maintenance obinutuzumab every 8 weeks for an additional 24 months (eg, maximum total duration of obinutuzumab of approximately 30 months [maximum 20 doses]).

At the discretion of the investigator, patients in arm B will be eligible to receive crossover treatment with zanubrutinib plus obinutuzumab if they experience progressive disease or their disease does not respond to therapy with a complete response (CR) or partial response (PR) after 12 months. This must be confirmed by independent central review. For patients who initiate crossover treatment with zanubrutinib plus obinutuzumab, safety, laboratory, and response evaluation assessments will continue to be performed per the Schedule of Assessments.

Study Assessments

Assessments of follicular lymphoma status during the study include: disease-related constitutional symptoms, physical examination of lymph nodes, liver, and spleen, complete blood count (CBC), bone marrow examination, positron emission tomography (PET)/computed tomography (CT) scan with contrast of neck, chest, abdomen, and pelvis, patient-reported outcomes (PROs; EQ-5D-5L and EORTC QLQ-C30 questionnaires).

Tumor assessments, including imaging studies, will be performed at screening, every 12 weeks from Cycle 1 Day 1 for 24 months, then every 24 weeks for 24 months, and then yearly until disease progression. All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. All patients must undergo PET-CT scan during screening. Patients whose disease is not [18F]fluorodeoxyglucose (FDG)-avid at screening will be followed by CT-based assessments alone. Patients whose disease is FDG-avid at screening will be followed by an integration of PET-CT and CT-based assessments as follows:

- PET-CT scans are required at screening, end of Cycles 3, 6, and 12, and to confirm a result on CT scan (CR/PR or disease progression)
- CT scans with contrast are required at all other tumor response assessments

Patients receiving zanubrutinib should remain on study treatment until disease progression is confirmed by independent central review. Patients receiving obinutuzumab should remain on study treatment until either disease progression is confirmed by independent central review or approximately 30 months of treatment with obinutuzumab (maximum 20 doses), whichever occurs first.

Assessments of safety will include adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, physical examinations, and vital signs. AEs will be graded for severity per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). An independent data monitoring committee (DMC) will periodically monitor safety data.

Key Eligibility Criteria:

The patients to be included in this trial will have a histologically confirmed diagnosis of B-cell follicular lymphoma (Grade 1, 2 or 3a) based on the World Health Organization (WHO) 2008 classification of tumors of hematopoietic and lymphoid tissue, the presence of measurable disease, and archival tissue available confirming diagnosis of B-cell follicular lymphoma. Patients must have received ≥ 2 prior systemic treatments for follicular lymphoma (including an anti-CD20 antibody and an appropriate alkylator-based combination therapy). Patients will have no currently active clinically significant cardiovascular disease, and no active infection with hepatitis B or C or HIV.

Test Product, Dose, and Mode of Administration:

Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients will take zanubrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Zanubrutinib capsules should not be opened, broken, or chewed at any time.

Reference Therapy, Dose, and Mode of Administration:

Obinutuzumab will be administered 1,000 mg intravenously on days 1, 8, and 15 of Cycle 1, then 1,000 mg on Day 1 of Cycles 2 to 6, then 1,000 mg every 8 weeks. (At the discretion of the investigator, obinutuzumab may be administered 100 mg on Day 1 and 900 mg on Day 2 of Cycle 1 instead of 1,000 mg on Day 1 of Cycle 1.) Responding patients may continue to receive maintenance obinutuzumab every 8 weeks for an additional 24 months (eg, maximum total duration of obinutuzumab of approximately 30 months [maximum 20 doses]).

Obinutuzumab should be administered at a rate of 50 mg/hr. The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If no infusion reaction occurs during the Cycle 1 Day 1 infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr for all subsequent doses. Patients should be premedicated with acetaminophen, antihistamine, and a glucocorticoid before each obinutuzumab infusion.

Statistical Methods:

All efficacy analyses will be performed using the Intent-to-Treat (ITT) analysis set (all patients who are randomized to a treatment group).

Primary Efficacy Endpoint Analysis:

Primary inference of comparing overall response rate by independent central review will be based on a Cochran-Mantel-Haenszel test adjusted for the randomization factors (number of prior lines of therapy [2 to 3 vs > 3] and rituximab-refractory status [yes vs no]) in the ITT analysis set.

The null and alternative hypotheses for comparing overall response rate are as follows:

H_0: $ORR_A = ORR_B$

Ha: $ORR_A > ORR_B$

where ORR_A is the overall response rate in arm A (zanubrutinib plus obinutuzumab) and ORR_B is the overall response rate in arm B (obinutuzumab monotherapy). If the obtained one-sided p-value is ≤ 0.025, it will be concluded that the combination therapy of zanubrutinib plus obinutuzumab results in a statistically significantly increase in overall response rate versus obinutuzumab monotherapy; thereby demonstrating the superiority of arm A over arm B.

Secondary Efficacy Endpoint Analyses:

- Duration of response will be summarized only for patients who have achieved an objective response. The distribution of duration of response will be summarized for each treatment group by the Kaplan-Meier method.
- Progression-free survival (PFS) will be compared based on the log-rank test stratified by the randomization stratification factors (number of prior lines of therapy [2 to 3 vs > 3], rituximab refractory status [yes vs no], and geographic region [China vs ex-China]). The distribution of progression-free survival, including median progression-free survival and progression-free survival rate at selected timepoints, will be estimated using the Kaplan-Meier method for each arm.
- Overall survival between the 2 treatment groups will be compared using the same methods employed for the PFS comparison. The distribution of overall survival (including median and other quartiles) and overall survival rate at selected timepoints will be estimated by the Kaplan-Meier method
- Complete response rate and complete metabolic response rate will be calculated as the proportion of patients who reached best overall response of complete response (complete metabolic response) or higher. The complete response and complete metabolic response rate will be compared between treatment groups using Fisher's exact test.
- Time-to-response will be summarized only for responders by sample mean, median and standard deviation for each treatment group.
- The EORTC QLQ-C30 and EQ-5D-5L questionnaires will be utilized. The scores and their changes from baseline will be summarized and compared between two treatment groups

Exploratory Efficacy Endpoint Analysis:

- Overall response rate in arm B after crossover to arm A will be summarized descriptively.

Safety Analyses:

The Safety analysis set (all patients who received any dose of study medication) will be used for all safety analyses.

Drug exposure will be summarized by treatment group and study medication including duration, dosage, and dose intensity.

All treatment-emergent AEs will be summarized. SAEs, deaths, treatment-emergent AEs ≥ Grade 3, study drug-related treatment-emergent AEs, treatment-emergent AEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

Pharmacokinetic Analyses:

Blood samples to assess plasma zanubrutinib concentrations will be collected in patients in arm A. Plasma zanubrutinib concentrations will be summarized by scheduled time of collection. A population pharmacokinetics (PK) analysis may be performed to include plasma concentrations of zanubrutinib from this trial in an existing model. PK parameters such as apparent clearance of the drug from plasma and $AUC_{0\text{-}12}$ may be derived from the population PK analysis if supported by data.

An exposure-response (efficacy or safety endpoints) analysis may be performed if supported by data. The results from the population PK and exposure-response analyses may be reported separately from the Clinical Study Report.

Sample Size Considerations:

The sample size calculation is based on the comparison of the primary endpoint of ORR in the ITT analysis set. Assuming ORR_A=0.55 and ORR_B=0.30, 210 patients will be enrolled in a 2:1 ratio (140 patients in arm A and 70 patients in arm B) to provide a power of approximately 91% in testing ORR_A versus ORR_B using a normal approximation to binomial distribution with a 2-sided significance level of 0.05 with continuity correction. The sample size calculation is based on methods in Hulley et al, 2013 and Fleiss et al, 1980.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BGB-3111	zanubrutinib
BTK	Bruton tyrosine kinase
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDG	[18F]fluorodeoxyglucose
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board

IRT	Interactive Response Technology
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLL	small lymphocytic lymphoma
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

1.1. Follicular Lymphoma

Follicular lymphoma is well characterized by its clinical presentation (primarily lymph node enlargement), its morphologic characteristics (preservation of follicular lymph node architecture despite infiltration with malignant lymphocytes), and its molecular features (over 90% of cases are associated with a specific translocation between the immunoglobulin heavy chain gene on chromosome 14 and the bcl-2 oncogene on chromosome 18). While there is considerable heterogeneity in the clinical course of follicular lymphoma, it is generally an indolent malignancy, with a prolonged but incurable clinical course. A cross-European registry study published in 2015, calculated a median age at onset of 62 years and an annual incidence of 5 cases per 100,000 population (Mounier et al 2015). Of note, the incidence of follicular lymphoma appears to be increasing significantly, from an estimated incidence of 2 to 3 cases/100,000 population in the 1950s.

Follicular lymphoma is classified by grade and stage. The World Health Organization (WHO) classification (Swerdlow et al 2008; Jaffe 2009) grades follicular lymphoma based on the number of blasts per high powered field, where Grade 1 is up to 5 blasts per high power field, and Grade 3b is more than 15, or a pure sheet of blasts. Grade 3b is considered to have a course identical to diffuse large B-cell lymphoma (DLBCL). The Ann Arbor staging system method is also used (National Comprehensive Cancer Network 2017; Dreyling et al 2017) to characterize follicular lymphoma by stage: stage I and II disease is considered localized, and may be suitable for local therapies such as involved field radiation therapy; whereas stage III and IV disease is considered widespread, and is managed with systemic therapies.

With modern chemoimmunotherapy for follicular lymphoma, median survival exceeds 10 years, except for the approximately 20% of patients with short remission duration following initial chemoimmunotherapy (Casulo et al 2015). In fact, over the past several decades, the incorporation of novel active agents into treatment practices for follicular lymphoma have resulted in a decline in lymphoma subtype-specific mortality trends (Howlader et al 2016). Yet, follicular lymphoma remains incurable, and the clinical history is typically one of multiple relapses, with successive treatment regimens resulting in progressively shorter disease-control intervals, until the emergence of fatal, resistant disease. In addition to the morbidity and mortality associated with treatment resistance, cumulative treatment-related toxicity (especially immunosuppression, myelosuppression, and secondary leukemia related to alkylator exposure), and transformation to DLBCL, remain significant contributors to mortality in patients with follicular lymphoma.

Therapeutic strategies in follicular lymphoma have been transformed in recent decades by the introduction of anti-CD20 monoclonal antibodies, used alone or as part of chemoimmunotherapy regimens. For patients with a high tumor burden, the progression-free survival (PFS) benefit of adding rituximab to cytotoxic chemotherapy has been clearly demonstrated in randomized trials (Hiddemann et al 2005; Herold et al 2007; Schulz et al 2007; Marcus et al 2016; Bachy et al 2013). The chemoimmunotherapy regimens, rituximab, cyclophosphamide, doxorubicin, and prednisolone; rituximab, cyclophosphamide, vincristine, and prednisolone; and bendamustine plus rituximab are all considered as treatment standards. Rituximab maintenance after initial chemoimmunotherapy has also been shown in phase 3 studies to improve PFS, but not overall

survival (OS; Sehn et al 2016). More recently, a phase 3 study has demonstrated that the second generation anti-CD20 antibody, obinutuzumab, plus chemotherapy, prolongs PFS as compared with rituximab plus chemotherapy (Marcus et al 2016), and thus obinutuzumab is likely to be added soon to expert guidelines as appropriate for initial therapy.

The treatment options are limited for patients with disease that has relapsed after or is refractory to chemoimmunotherapy. In the rituximab-refractory setting, obinutuzumab plus bendamustine prolongs PFS as compared with bendamustine alone (Sehn et al 2016). Idelalisib, a phosphoinositol-3-kinase inhibitor approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for follicular lymphoma under their respective, accelerated and conditional approval mechanisms in 2013, is considered an appropriate treatment option for patients who have received at least 2 prior systemic therapies (Zydelig Prescribing Information 2016; Zydelig Summary of Product Characteristics 2016). However, late-stage trials intended to confirm the clinical benefit of idelalisib in follicular lymphoma were terminated early because of an imbalance in infectious deaths in the idelalisib arms of these studies (Zydelig FDA Alerts 2016).

1.2. Inhibition of Bruton Tyrosine Kinase in Follicular Lymphoma

Inhibitors of Bruton tyrosine kinase (BTK) have been evaluated in follicular lymphoma and have shown modest single agent activity. The first generation BTK inhibitor ibrutinib was evaluated in a phase 2 trial in 110 patients with "chemoimmunotherapy-resistant" follicular lymphoma, defined as having received at least 2 prior lines of therapy and demonstrated progressive disease within 12 months of a chemoimmunotherapy regimen. In this study, the overall response rate (ORR) was 21% and the median duration of response was 19.4 months (Gopal et al 2016).

1.3. Zanubrutinib (BGB-3111)

Zanubrutinib, formerly designated as BGB-3111, is a potent, specific, and irreversible BTK inhibitor with a favorable pharmacologic and toxicologic profile. Zanubrutinib is different from ibrutinib in the following ways:

1. Zanubrutinib is more selective in the relative inhibition of BTK versus off-target tyrosine kinases, including EGFR, FGR, FRK, HER2, HER4, ITK, JAK 3, LCK, and TEC. This may reduce toxicities possibly due to off-target inhibition such as diarrhea, thrombocytopenia, bleeding, atrial fibrillation, rash, and fatigue;
2. Zanubrutinib has improved oral bioavailability;
3. Zanubrutinib displays significantly less inhibitory effect on rituximab-induced antibody-dependent cell-mediated cytotoxicity, and so is unlikely to adversely impact the antitumor effects of rituximab.

1.3.1. Summary of Relevant Nonclinical Data with Zanubrutinib

Summaries of nonclinical studies are provided below. For more detailed information please refer to the zanubrutinib Investigator Brochure.

Zanubrutinib is a potent, specific and irreversible BTK kinase inhibitor with a 50% maximum inhibitory concentration (IC_{50}) of 0.3 nM. Cellular assays confirm that zanubrutinib inhibits

B-cell receptor aggregation-triggered BTK autophosphorylation, and blocks downstream PLCγ2 signaling in mantle cell lymphoma cell lines. Zanubrutinib had an IC_{50} of 1.8 nM in a homogeneous time-resolved fluorescence-based BTKpY223 assay. It potently and selectively inhibited cellular growth of several mantle cell lymphoma cell lines (REC-1, Mino and JeKo-1) and the activated B-cell type DLBCL cell line TMD-8, with IC_{50} values from 0.36 nM to 20 nM, while it was inactive in many other hematologic cancer cell lines.

In vivo studies have demonstrated that zanubrutinib induces dose-dependent antitumor effects against REC-1 mantle cell lymphoma xenografts engrafted either subcutaneously or systemically in mice which are significantly more effective than ibrutinib. Zanubrutinib also demonstrated better antitumor activity than ibrutinib in TMD-8 DLBCL subcutaneous xenograft model. In a pharmacokinetic (PK)/pharmacodynamic study, oral administration of Zanubrutinib resulted in time-dependent occupancy of BTK in blood and in spleen in mice, and was approximately 3-fold more potent than ibrutinib in mouse pharmacodynamic assays.

In a panel of 342 human kinases, 1 μM zanubrutinib inhibited only 12 other kinases by > 70%. Zanubrutinib was more selective than ibrutinib for inhibition of kinase activity of BTK vs EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC. Cellular assays also confirmed that zanubrutinib is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Inhibition of ITK has been reported to reduce rituximab-induced antibody-dependent cell-mediated cytotoxicity. Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced antibody-dependent cell-mediated cytotoxicity, consistent with zanubrutinib being a more selective BTK inhibitor, with much weaker ITK inhibition activity than ibrutinib in both biochemical and cellular assays.

The toxicity profiles of zanubrutinib have been well characterized in rats and dogs. No specific safety concerns were identified in vital organs/systems including cardiovascular system, respiratory system, and central nervous systems. No QTc changes were noted in the conscious telemetry-implanted dogs over 24 hours after dosing up to 100 mg/kg, or in the repeat dose toxicity studies in dogs over 91 days at doses up to 100 mg/kg/day. No mortality or severe toxicity was noted in 91-day repeat dose toxicity studies in both rats and dogs at doses up to 300 mg/kg and 100 mg/kg, respectively. Test article-related reversible histopathology changes were mainly noted in rats, including pancreas, spleen, prostate gland, cecum, colon, rectum, skin (lip and/or nose), and uterus. None of the above findings were considered to be adverse in the 91-day repeated dosing studies. No genotoxicity was noted in the genotoxicity core battery studies.

1.3.2. Summary of Relevant Clinical Experience with Zanubrutinib

1.3.2.1. Dose Selection for Zanubrutinib

In the first-in-human, phase 1 study, zanubrutinib -AU-003, the PK of zanubrutinib was linear between 40 mg and 320 mg once a day administered orally (BeiGene Investigator Brochure). The absorption of zanubrutinib is rapid with median time to maximum plasma concentration (C_{max}) of 2 hours. The terminal elimination half-life is approximately 4 hours at 320 mg once a day. Results from a food-effect study showed that zanubrutinib exposure was not altered by high-fat breakfast, and mean area under the plasma concentration-time curve (AUC) and C_{max} were increased by 12% and 51%, respectively with standard breakfast when compared with

fasting. The magnitude of increase in exposure with food was well within doubling of exposure associated with 320 mg administered once a day in the ongoing phase 1, and was not associated with any new safety findings. Therefore, zanubrutinib can be administered with or without food.

Full occupancy of BTK in peripheral blood mononuclear cells was achieved in all patients in the BGB-3111-AU-003 study, while occupancy in lymph node tissue was assessed only at 160 mg twice a day and 320 mg once a day (Tam et al 2015). At the 160 mg twice a day dose, full BTK occupancy was observed at trough, suggesting that sustained target occupancy could be achieved in disease-originating tissues, thus more efficiently inhibiting BTK on a continuous basis, further preventing breakthrough signaling despite cycles of new BTK synthesis. Activity has been observed across various B-cell malignancies (including chronic lymphocytic leukemia [CLL], mantle cell lymphoma, Waldenstrom macroglobulinemia, and follicular lymphoma) at all tested dose levels; thus, a minimum effective dose cannot be established at this time. Conversely, there is now extensive experience at the 160 mg twice a day and 320 mg once a day dose; both schedules show a high level of activity without compromising the tolerability profile as compared with lower doses of zanubrutinib. Therefore, the dose of 160 mg administered orally twice a day has been selected as the recommended phase 2 and phase 3 dose based on sustained target occupancy, high rates of objective response in multiple types of B-cell malignancies, and a favorable safety and tolerability profile.

1.3.2.2. Preliminary Efficacy and Safety Data with Zanubrutinib

There are two relevant studies of zanubrutinib that provide efficacy and safety data, the first-in-human study, BGB-3111-AU-003, and the combination study, BGB-3111-GA101-001.

The BGB-3111-AU-003 study is an open-label, dose-escalation and dose-expansion study of zanubrutinib monotherapy that was initiated in Australia in August 2014. The study consists of two parts. In part 1, the primary objectives are to determine the safety and tolerability of zanubrutinib in patients with various B-cell malignancies (CLL/small lymphocytic lymphoma [SLL], non-Hodgkin lymphoma [NHL], and Waldenstrom macroglobulinemia [WM]) and determine the recommended phase 2 dose. In part 2, the primary objective is to further assess the safety and tolerability of zanubrutinib in patients with B-cell malignancies, while a secondary objective is to assess the anti-tumor activity of zanubrutinib at the recommended phase 2 dose.

In the BGB-3111-AU-003 CLL/SLL cohort, as of 03 October 2016, 46 patients were followed up for at least 12 weeks. Zanubrutinib was well tolerated, with 65% of patients reporting no drug-related adverse events (AEs) > Grade 2 severity. The most frequent AEs of any attribution were petechiae or purpura or contusion (combined events, 22 patients; 48%), upper respiratory tract infection (33%; all Grade 1 or 2), fatigue (28%; all Grade 1 or 2), diarrhea, cough, and headache (all 20%; all Grade 1 or 2). There were 3 serious adverse events (SAEs) assessed as possibly related to zanubrutinib (Grade 2 cardiac failure, Grade 2 pleural effusion and Grade 3 purpura). After a median follow-up of 8.6 months (range, 2.2 to 20.9 months), the ORR was 96% (44/46), with a partial response (PR) rate of 67% (31/46), partial response with lymphocytosis rate of 28% (13/46), and stable disease (SD) rate of 2% (1/46). Of the 8 patients with measurable disease at baseline, their tumor volume (sum of product diameters) decreased from 60% to 100% with a median decrease of 86%. No instances of disease progression or Richter's transformation have occurred.

In the BGB-3111-AU-003 Waldenstrom macroglobulinemia cohort, as of 31 December 2016, 46 patients were enrolled. The most frequent AEs reported (all were Grade 1 or 2) were: upper respiratory infection (33%), contusion (28%), and constipation (22%). There were 3 treatment-related SAEs (Grade 2 atrial fibrillation, Grade 2 headaches, Grade 3 cryptococcal meningitis); in all 3 cases, zanubrutinib was withheld and safely resumed. Three patients developed atrial fibrillation (one Grade 1, two Grade 2, all events in patients without a previous history of atrial fibrillation), and 1 patient reported Grade 3 diarrhea. No serious hemorrhage was reported. Two patients have discontinued zanubrutinib for AEs, 1 with an exacerbation of pre-existing bronchiectasis and 1 with prostate cancer. The ORR was 93% (38/41); with a major response rate of 78% (32/41), including very good partial response rate of 39% (16/41) and PR rate of 39% (16/41). In patients with hemoglobin < 10 g/dL at baseline, hemoglobin increased from a median of 8.8 g/dL to 13.8 g/dL and serum immunoglobulin M decreased from a median of 32.5 g/L at baseline to 5.4 g/L. Of the 16 patients with lymphadenopathy at baseline, the median decrease in lymphadenopathy (measured as median reduction in sum of product diameters) was 38% (9% to 81%).

The BGB-3111-GA101-001 study is an ongoing, open-label, multicenter, phase 1b study of the combination of zanubrutinib and obinutuzumab in patients with various B-cell malignancies. As of 15 December 2016, 40 patients with CLL/SLL (17 patients with previously untreated disease; 23 patients with relapsed/refractory disease), and 13 patients with relapsed or refractory follicular lymphoma were enrolled. The median follow-up time was 4.1 months for CLL/SLL and 6.2 months for follicular lymphoma. Zanubrutinib plus obinutuzumab was well tolerated. No fatal AEs occurred; only 1 AE led to treatment discontinuation (squamous cell carcinoma in a patient with prior squamous cell carcinoma). SAEs were reported in 25.0% of the patients with CLL/SLL and 23.1% of the patients with follicular lymphoma; there was only 1 SAE related to obinutuzumab (infusion-related reaction) and 1 SAE related to zanubrutinib (pneumonia). There were no AEs of atrial fibrillation. Patients were evaluable for response if they had completed baseline and ≥ 1 on-treatment response assessment. ORRs were 88.9% in previously untreated CLL/SLL, 86.7% in relapsed/refractory CLL/SLL, and 81.8% in relapsed/refractory follicular lymphoma, including 3 complete responses (CRs) in CLL/SLL and 5 CRs in follicular lymphoma. Two patients experienced disease progression (1 with relapsed/refractory CLL, 1 with relapsed/refractory follicular lymphoma); no instances of disease transformation occurred. For more detailed information on the clinical experience for zanubrutinib please refer to the Investigator Brochure (BeiGene Investigator Brochure).

1.3.2.3. Safety Pharmacology

The potential risk of zanubrutinib on QT interval prolongation was assessed using a battery of preclinical studies and a clinical thorough QT study (BGB-3111-106). A GLP-compliant hERG assay was conducted. Based on the clinical steady-state, unbound C_{max} of 0.042 μM (total C_{max} 346 ng/mL; plasma protein binding 94.2%) observed at the recommended Phase 2 dose (RP2D) of 160 mg BID, there is more than a 200-fold exposure margin compared with the hERG IC_{50} of 9.11 μM.

No effects on blood pressure, heart rate, or electrocardiogram (ECG) findings, including QT and QTc intervals, were noted in telemetry-instrumented conscious dogs following single doses of zanubrutinib up to 100 mg/kg. In addition, no abnormal changes in ECG or cardiovascular

function were noted in 28- and 91-day repeat-dose toxicity studies in dogs at doses up to 100 mg/kg. In these studies, the systemic exposure of zanubrutinib was 10-fold higher than that observed at the human therapeutic dose.

The QT interval prolongation potential of zanubrutinib was evaluated in healthy subjects in a thorough QT study (BGB-3111-106). Results from this study demonstrated that single oral doses of zanubrutinib at a therapeutic dose of 160 mg and a supratherapeutic dose of 480 mg did not have a clinically relevant effect on ECG parameters, including QTc intervals and other ECG intervals. Because of the short half-life and no accumulation seen upon multiple-dosing, these results are also applicable for steady-state conditions.

1.3.2.4. Clinical Pharmacology

Results from a dedicated drug-drug interaction study (BGB-3111-104) indicate that co-administration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg once daily for 8 days) decreased exposure of zanubrutinib by 13.5-fold for $AUC_{0-\infty}$, and 12.6-fold for C_{max}, in healthy subjects. Co-administration of zanubrutinib with the strong CYP3A inhibitor itraconazole (200 mg once daily for 4 days) increased exposure of zanubrutinib by 3.8-fold for $AUC_{0-\infty}$, and 2.6-fold for C_{max}. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib. Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Appendix 8 for a list of these medications) and grapefruit juice and Seville oranges should be done with caution, as they may affect the metabolism of zanubrutinib. If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification table in Appendix 8. The medical monitor should be consulted in these situations.

Zanubrutinib is a mild inducer of CYP3A4 and CYP2C19. Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs. Since blood levels and effectiveness of drugs that are substrates for CYP3A (eg, steroidal contraceptives) may be reduced by CYP3A inducers, if patients are using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must be used. The coadministration of oral P-glycoprotein (P-gp) substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.

1.4. Benefit-Risk Assessment

A pooled safety analysis of ongoing zanubrutinib clinical trials using a data cutoff of September 2017 provides data for 641 subjects receiving zanubrutinib either as monotherapy or in combination with other agents following a mean exposure time of 7.7 months. Historically, the class of BTK inhibitors has raised some safety concern, particularly regarding the potential for serious hemorrhage and cardiac rhythm disturbance with atrial fibrillation or flutter being the most common events. The pooled analysis of zanubrutinib safety data shows atrial fibrillation was 1.7% and serious hemorrhage was 1.9%; both of these values are close to expected background rates. Concomitant use of vitamin K antagonists was, and continues to be, allowed

in zanubrutinib trials. No new safety or tolerability signals have been observed and there have been few instances of drug discontinuation for any adverse event (Tam et al 2017).

The current randomized Phase 2 study is based on results from a global Phase 1b, open-label, multicenter study of the combination of zanubrutinib and obinutuzumab in patients with B-cell malignancies—specifically, CLL/SLL, WM, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, and DLBCL. The primary objectives in this study were to evaluate the safety and tolerability for the combination of zanubrutinib and obinutuzumab. The first patient was dosed on 13 January 2016 and, as of the 16 September 2018 data cutoff, a total of 119 patients had been treated on study. Adverse events ≥ Grade 3, regardless of attribution by the investigator, included: neutropenia in 28 subjects (23.5%), fatigue in 1 (0.8%), thrombocytopenia in 9 (7.6%), pyrexia in 3 (2.5%), back pain in 3 (2.5%), constipation in 1 (0.8%), pneumonia in 6 (5.0%) and urinary tract infection in 3 subjects (2.5%). Seven subjects (5.9%) had an adverse event leading to treatment discontinuation. No new safety signals or trends have been observed with the combination therapy of zanubrutinib and obinutuzumab.

Given the safety summary profile for zanubrutinib, either as monotherapy or in combination with obinutuzumab, BeiGene believes that the benefit-risk balance remains favorable for research subjects.

2. STUDY OBJECTIVES

All primary and secondary objectives will compare zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy.

Primary:

- To evaluate efficacy, as measured by overall response rate determined by independent central review

Secondary:

- To evaluate efficacy, as measured by the following:
  - Overall response rate determined by investigator assessment
  - Duration of response determined by independent central review and by investigator assessment
  - Progression-free survival determined by independent central review and by investigator assessment
  - Overall survival
  - Rate of complete response or complete metabolic response determined by independent central review and by investigator assessment
  - Time to response determined by independent central review and by investigator assessment
  - Patient-reported outcomes
- Safety and tolerability
- Pharmacokinetics (zanubrutinib plus obinutuzumab arm only)

Exploratory:

- Overall response rate in obinutuzumab arm after crossover to receive zanubrutinib plus obinutuzumab

3. STUDY DESIGN

3.1. Summary of Study Design

This is an international (approximately 100 sites), phase 2, open-label, randomized, active-control study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in 210 patients with relapsed or refractory follicular lymphoma. The primary efficacy endpoint is ORR determined by independent central review. Disease response will be assessed per the Lugano Classification for Non-Hodgkin Lymphoma (NHL) (Cheson et al 2014; Appendix 2) - hereafter referred to as Lugano Classification for NHL.

Central randomization (2:1) will be used to assign patients to one of the following study drug treatments:

Arm A: zanubrutinib plus obinutuzumab

Arm B: obinutuzumab monotherapy

Randomization will be stratified by the number of prior lines of therapy (2 to 3 versus > 3), rituximab-refractory status (yes vs no), and geographic region (China vs ex-China). Rituximab-refractory is defined as follows: "Failure to respond to, or progression during, any previous rituximab-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab dose, in the induction or maintenance treatment settings." Rituximab-containing regimen is defined as those with at least four weekly doses of rituximab if administered as monotherapy, or at least four cycles if given as chemoimmunotherapy. For induction therapy regimens during which a patient had disease progression, the minimum necessary rituximab dose is one full cycle (monotherapy or chemoimmunotherapy) or one dose of 375 mg/m^2 (maintenance). A patient who has not received any prior rituximab will have a rituximab-refractory status of "NO" for stratification.

Treatment with zanubrutinib plus obinutuzumab and treatment with obinutuzumab monotherapy will be open label. Study treatment must commence within 5 days after randomization.

Each cycle consists of 28 days. Study drug treatments will be administered as follows, depending on cohort and treatment assignment:

- Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food.
- Obinutuzumab will be administered 1,000 mg intravenously on days 1, 8, and 15 of Cycle 1, then 1,000 mg on Day 1 of Cycles 2 to 6, then 1,000 mg every 8 weeks. (At the discretion of the investigator, obinutuzumab may be administered 100 mg on Day 1 and 900 mg on Day 2 of Cycle 1 instead of 1,000 mg on Day 1 of Cycle 1.) Responding patients may continue to receive maintenance obinutuzumab every 8 weeks for an additional 24 months (eg, maximum total duration of obinutuzumab of approximately 30 months [maximum 20 doses]).
- At the discretion of the investigator, patients in arm B will be eligible to receive crossover treatment with zanubrutinib plus obinutuzumab if they experience progressive disease or their disease does not respond to therapy with a CR or PR after 12 months. This must be confirmed by independent central review. For patients who

initiate crossover treatment with zanubrutinib plus obinutuzumab, safety, laboratory, and response evaluation assessments will continue to be performed per the Schedule of Assessments (Appendix 9).

Study Assessments

Assessments of follicular lymphoma status during the study include: disease-related constitutional symptoms, physical examination of lymph nodes, liver, and spleen, complete blood count (CBC), bone marrow examination, positron emission tomography (PET)/computed tomography (CT) scan with contrast of neck, chest, abdomen, and pelvis, patient-reported outcomes (PROs; EQ-5D-5L and EORTC QLQ-C30 questionnaires).

Tumor assessments, including imaging studies, will be performed at screening, every 12 weeks from Cycle 1 Day 1 for 24 months, then every 24 weeks for 24 months, and then yearly until disease progression. All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. All patients must undergo PET-CT scan during screening. Patients whose disease is not FDG-avid at screening will be followed by CT-based assessments alone. Patients whose disease is FDG-avid at screening, by either site assessment or the central imaging vendor, will be followed by an integration of PET-CT and CT-based assessments as follows:

- PET-CT scans are required at screening, end of Cycles 3, 6, and 12, and to confirm a result on CT scan (CR/PR or disease progression)
- CT scans with contrast are required at all other tumor response assessments

Patients receiving zanubrutinib should remain on study treatment until disease progression is confirmed by independent central review. Patients receiving obinutuzumab should remain on study treatment until either disease progression is confirmed by independent central review or approximately 30 months of treatment with obinutuzumab (maximum 20 doses), whichever occurs first.

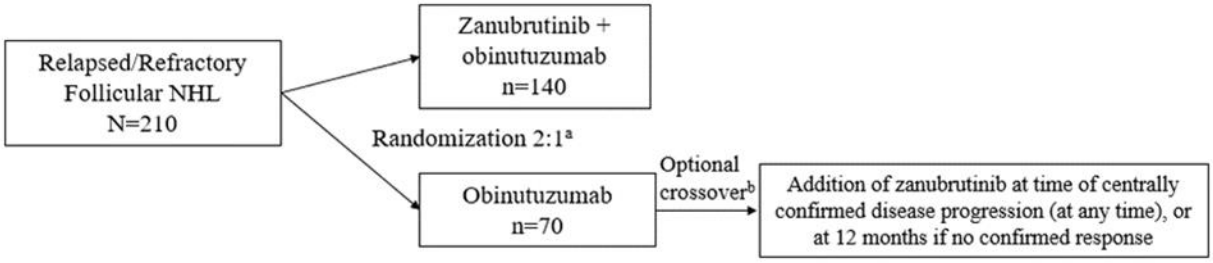
Assessments of safety will include AEs, SAEs, clinical laboratory tests, physical examinations, and vital signs. AEs will be graded for severity per the current version of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE). An independent data monitoring committee (DMC) will periodically monitor safety data.

Components of the Follicular Lymphoma International Prognostic Index (FLIPI) score (Solal-Céligny et al 2004) at diagnosis and at screening will be collected: age, Ann Arbor stage, hemoglobin level, number of nodal areas (see Appendix 3), and serum LDH level, in addition to the following components of FLIPI 2 (Relander et al 2010): bone marrow involvement, nodes > 6 cm, and β_2-microglobulin.

3.2. Study Schema

The study schematic is provided in Figure 1.

Figure 1. Study Schema



Abbreviation: NHL, non-Hodgkin lymphoma.
[a] Randomization stratified by the number of prior lines of therapy (2 to 3 vs > 3), rituximab-refractory status (yes vs no), and geographic region (China vs ex-China).
[b] Option for addition of zanubrutinib following independent central confirmation of disease response status.

3.3. Blinding

Treatment with zanubrutinib and obinutuzumab will be open label, however, the assessment of overall response rate by independent central review (primary endpoint) will be blinded.

3.4. Duration of Study

The total duration of this study is expected to be approximately 5 years, assuming an expected enrollment duration of 30 months and maximum duration of obinutuzumab of approximately 30 months (maximum 20 doses) after the last enrolled patient. Patients assigned to arm A (zanubrutinib plus obinutuzumab), who in the opinion of the investigator, continue to benefit from study treatment may continue treatment with zanubrutinib by enrolling on the zanubrutinib Long Term Extension Study; this is a rollover study for patients who wish to continue receiving zanubrutinib.

3.5. Discussion of Study Design, Including Choice of Control Group

The proposed study will be conducted in patients with histologically confirmed follicular lymphoma (Grade 1, 2, or 3a) who have received ≥ 2 prior systemic treatments for follicular lymphoma; have received an anti-CD20 antibody, and an appropriate alkylator-based combination therapy (eg, rituximab, cyclophosphamide, doxorubicin, and prednisolone; rituximab, cyclophosphamide, vincristine, and prednisolone; and/or bendamustine plus rituximab).

The patient eligibility definition above is intended to define a patient population for whom new, effective treatments are needed. While current expert guidelines specify the repeat use of chemoimmunotherapy for patients with a long (≥ 24 months) remission to their prior therapy, acceptable options for patients with a short remission to prior therapy are quite limited. Additionally, many treatments are not applicable to patients with follicular lymphoma in later relapse due to age, non-lymphoma comorbidity, limited bone marrow reserve due to prior cytotoxic therapy or stem cell transplantation, or radioimmunotherapy treatments

(National Comprehensive Cancer Network 2017; Dreyling et al 2017). For many patients with follicular lymphoma in later relapse, and particularly those with short response duration to prior therapy, this leaves anti-CD20 antibody therapy or idelalisib as palliative options.

According to the European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow-up of newly diagnosed and relapsed follicular lymphoma (Dreyling et al 2017): "the selection of salvage treatment depends on efficacy of prior regimens…obinutuzumab has recently received a positive recommendation for approval by the European Medicines Agency for rituximab-refractory cases based on an improved PFS in comparison with bendamustine only." In Europe, the anti-CD20 agent, obinutuzumab (Gazyvaro®) has gained approval in the rituximab-refractory setting (Gazyvaro Summary of Product Characteristics 2016), when added to bendamustine, based on demonstration of prolonging PFS compared with bendamustine-alone in patients who were refractory to their prior rituximab-containing treatment (Sehn et al 2016). In the context of the proposed trial in the third-line and beyond setting, the use of obinutuzumab monotherapy as a comparator would be appropriate given the likelihood that prior bendamustine-based therapy will already have been administered or considered, and the ability to re-administer anti-CD20 monotherapy remains a palliative measure in the majority of patients with relapsed or refractory disease. Furthermore, the use of obinutuzumab rather than rituximab would allow for a direct measure of the contribution of obinutuzumab to the safety and activity of the novel combination regimen under investigation (zanubrutinib plus obinutuzumab).

Obinutuzumab has also been evaluated as a single-agent in relapsed or refractory follicular lymphoma/indolent lymphoma. In a randomized phase 2 study of obinutuzumab versus rituximab in rituximab-sensitive, relapsed indolent lymphoma, defined as having a documented response lasting at least 6 months from the last rituximab dose, obinutuzumab was associated with a higher response rate (45% versus 27%) compared with rituximab, but there was no difference in median or 2-year PFS (Sehn et al 2015). In a previous phase 1 study, obinutuzumab demonstrated a 23% ORR rate in 23 patients with relapsed or refractory indolent lymphoma, with a 15% response rate in a subset of 13 patients with rituximab-refractory disease, defined as progressive disease within 12 months of previous rituximab therapy (Sehn et al 2012). In the phase 3 GALLIUM study in patients with previously untreated follicular lymphoma, obinutuzumab-chemotherapy induction followed by obinutuzumab maintenance prolonged PFS as compared with rituximab-chemotherapy induction followed by rituximab maintenance (Marcus et al 2016).

The phosphoinositol-3-kinase inhibitor idelalisib (Zydelig®) was approved by the EMA for use in patients with follicular lymphoma refractory to 2 prior lines of treatment, based on results from a single-arm, multicenter clinical study conducted in 125 patients with indolent lymphoma (Zydelig Summary of Product Characteristics 2016). The study population included 72 patients with follicular lymphoma. All patients were refractory to rituximab, defined per protocol as less than a PR or disease progression within 6 months after completion of a prior therapy. The ORR was 57% (54% in follicular lymphoma), with 6 patients (8%; all with follicular lymphoma) achieving a CR. The median duration of response was 12.5 months.

Despite this initial promising data, three phase 3 trials of idelalisib in indolent lymphoma, in combination with anti-CD20 agents or chemoimmunotherapy, were prematurely terminated due to an imbalance in infectious deaths in the idelalisib arms of the studies (Zydelig FDA

Alerts 2016). Thus, we believe that treatments capable of inducing a high rate of durable responses, with favorable safety profiles, in patients with follicular lymphoma or indolent lymphoma in second or greater relapse, are still needed; particularly those patients who are now treatment-refractory or have a short remission duration with prior therapy.

The patient population selected for this phase 2 study will have received standard treatment options with chemoimmunotherapy approaches and will have failed their last therapy. This represents a follicular lymphoma population with a high unmet medical need. Patients who have failed, or who have been considered unsuitable for idelalisib, and who would be appropriate to receive palliative anti-CD20 therapy with obinutuzumab will be enrolled.

The early results of the combination of zanubrutinib and obinutuzumab are promising with regard to the frequency of objective response, depth of response, lack of treatment failure due to progressive disease or toxicity, and tolerability/safety profile. Though the incorporation of chemoimmunotherapy into the sequential treatment practice for follicular lymphoma has improved lymphoma-specific outcomes in this disease, follicular lymphoma remains incurable, and the incorporation of cytotoxic agents into the treatment sequence for follicular lymphoma, particularly alkylating agents, can result in cumulative myelotoxicity, immunosuppression, and risk for secondary leukemia; therefore, it is reasonable to evaluate regimens such as zanubrutinib plus obinutuzumab as potential alternatives to cytotoxic chemoimmunotherapy regimens.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all of the following criteria:

1. ≥ 18 years of age at the time of informed consent
2. Histologically confirmed diagnosis of B-cell follicular lymphoma (Grade 1, 2 or 3a) based on the WHO 2008 classification of tumors of hematopoietic and lymphoid tissue
3. ≥ 2 prior systemic treatments for follicular lymphoma
4. Previously received an anti-CD20 antibody and an appropriate alkylator-based combination therapy, including:
    a. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
    b. Rituximab, cyclophosphamide, vincristine, and prednisolone
    c. Bendamustine plus rituximab
5. Disease progression after completion of most recent therapy or refractory disease, defined as failure to achieve CR or PR to most recent therapy, and most recent therapy was an appropriate second-line (or later) systemic therapy for follicular lymphoma
6. Presence of measurable disease, defined as ≥ 1 nodal lesion that is > 2 cm in longest diameter, or ≥ 1 extranodal lesion that is > 1 cm in longest diameter
7. Availability of archival tissue confirming diagnosis of B-cell follicular lymphoma (or if archival tissue is not available, a copy of the pathology report confirming diagnosis of B-cell follicular lymphoma is required)
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
9. Life expectancy ≥ 6 months
10. Adequate organ function defined as:
    a. Absolute neutrophil count (ANC) ≥ 1000/mm^3, except when neutropenia is assessed by the investigator to be directly due to active lymphoma, in which case ANC must be ≥ 750/mm^3
    b. Platelet > 50,000/mm^3 (without growth factor support or transfusion within 7 days)
    c. Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault or MDRD equation or as measured by nuclear medicine scan or 24-hour urine collection)
    d. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase, and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤ 3.0 x upper limit of normal (ULN)
    e. Serum total bilirubin < 2.0 x ULN (unless documented Gilbert's syndrome)
11. Female patients of childbearing potential, must practice highly effective methods of contraception initiated prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, or 18 months after the last dose of obinutuzumab, whichever is longer. A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral

salpingectomy and bilateral oophorectomy. Highly effective contraceptive methods include the following:

a. Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation
   - Oral, intravaginal or transdermal
b. Progestogen-only hormonal contraception associated with the inhibition of ovulation
   - Oral, injectable, implantable
c. An intrauterine device
d. Intrauterine hormone-releasing system
e. Bilateral tubal occlusion
f. Vasectomized partner
g. Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day prior to first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, or 18 months after the last dose of obinutuzumab, whichever is longer). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, and withdrawal are not acceptable methods of contraception.
   Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be used in combination with another acceptable method listed above.

For patients using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must be used.

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

12. Male patients are eligible if abstinent (as defined above), vasectomized, or if they agree to the use of barrier contraception in combination with other methods described above during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib, or 18 months after the last dose of obinutuzumab, whichever is longer.
13. Ability to provide written informed consent and can understand and comply with the requirements of the study.

4.2. Exclusion Criteria

Each patient eligible to participate in this study must NOT meet any of the following exclusion criteria:

1. Known central nervous system involvement by leukemia or lymphoma
2. Evidence of transformation from follicular lymphoma to DLBCL or other aggressive histology (such as large cells seen on biopsy or high PET avidity in a single node seen on PET scan)
3. Allogeneic hematopoietic stem cell transplantation within 12 months of study enrollment
4. Prior exposure to a BTK inhibitor
5. Prior malignancy within the past 2 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 prostate cancer
6. Clinically significant cardiovascular disease including the following:
    a. Myocardial infarction within 6 months before screening
    b. Unstable angina within 3 months before screening
    c. New York Heart Association Class III or IV congestive heart failure (see Appendix 4)
    d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
    e. QTcF > 480 milliseconds based on Fridericia's formula
    f. History of Mobitz II second-degree or third degree heart block without a permanent pacemaker in place
    g. Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mmHg and diastolic blood pressure > 105 mmHg at screening
7. History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
8. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug
9. Severe or debilitating pulmonary disease
10. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
11. Active fungal, bacterial and/or viral infection requiring systemic therapy
12. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of safety or efficacy results

13. Known infection with HIV, or serologic status reflecting active hepatitis B or C infection as follows:
    a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable (< 20 IU/mL), and if they are willing to undergo monthly monitoring for HBV reactivation.
    b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable (<15 IU/mL).
14. Major surgery within 4 weeks of the first dose of study drug
15. Pregnant or lactating women
16. Vaccination with a live vaccine within 35 days prior to the first dose of study drug
17. Ongoing alcohol or drug addiction
18. Hypersensitivity to zanubrutinib or obinutuzumab or any of the other ingredients of the study drugs
19. Requires ongoing treatment with a strong CYP3A inhibitor or inducer
20. Concurrent participation in another therapeutic clinical trial.
21. Requires ongoing need for corticosteroid treatment. NOTE: Systemic corticosteroids must be fully tapered off/stopped at least 5 days before the day of first study drug.

5. ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is provided in the Schedule of Assessments (Appendix 9).

Visit Windows

A study visit may be scheduled on any day within a specified study week. For any given day within the study week, the visit window is ± 7 days (ie, 7 days before or after the given day) unless otherwise stated. Study drug supplies must be considered when scheduling visits during windows. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

Informed Consent

At the screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted (unless the procedures are part of routine standard of care), and must document the informed consent process in the patient's clinical record. Informed consent may be obtained before the 35-day screening period. Consent must be obtained using the most current version of the form approved by the ethics committee.

Repeating the screening procedures or tests is allowed if the patient did not previously meet the inclusion and exclusion criteria or if needed in order to have a documented result within the protocol-specified screening window.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent before randomization, study site personnel should document the screen failure in the patient's source documents. The documentation should include demographics and medical history, the reason for screen failure, the eligibility criteria reviewed, procedures performed, etc.

5.1. Enrollment and Randomization

All screening procedures must be performed up to 35 days before the first administration of study drug, unless noted otherwise; assessments not completed within this interval must be repeated. The site investigator is responsible for maintaining a record of all patients screened and those who are enrolled in the study.

Patient Numbering

After obtaining informed consent, study site personnel will access the Interactive Response Technology (IRT) system to assign a unique patient number to a potential study participant. Patient numbers will be assigned in chronological order starting with the lowest number. Once a patient number has been assigned to a patient, it cannot be reassigned to any other patient.

Medical and Cancer History

Review any medical and cancer history any time after obtaining informed consent; includes presence or absence of disease-related constitutional symptoms. Clinically significant medical history findings (ie, previous diagnoses, diseases or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the patient's

study eligibility will be collected and captured in the electronic case report form (eCRF). Clinically significant is defined as any events, diagnoses or laboratory values requiring treatment, follow-up or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities.

Other background information to be collected includes: history of disease (including the date of initial diagnosis and current disease status), staging, sites of disease, and presence or absence of disease-related constitutional symptoms. Prior medications/significant non-drug therapies and demographic data (gender, date of birth [or age] and race/ethnicity) will also be collected.

Components of the Follicular Lymphoma International Prognostic Index (FLIPI) score (Solal-Céligny et al 2004) at diagnosis and at screening will be collected: age, Ann Arbor stage, hemoglobin level, number of nodal areas (see Appendix 3), and serum LDH level, in addition to the following components of FLIPI 2 (Relander et al 2010): bone marrow involvement, nodes > 6 cm, and β_2-microglobulin.

Confirmation of Eligibility

The investigator will assess and confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

After a patient is screened and the investigator determines the patient is eligible for randomization, study site personnel will complete an Eligibility Authorization Packet and email it to the medical monitor or designee to approve the enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Packet is in the patient's file before proceeding with study procedures.

The archival tissue sample used for follicular lymphoma diagnosis or the associated pathology report from diagnosis will be sent to the central pathology laboratory for confirmation of tissue diagnosis. It is not required that the archival tissue sample or pathology report be sent before randomization/treatment assignment, but documentation must be provided as part of the eligibility package.

Enrollment/Randomization

Access the IRT system to assign study drugs. This may occur up to 5 days before the day of first dose of study drug.

5.2. Electrocardiogram

Obtain per local practice and read locally to confirm eligibility. A 12-lead electrocardiogram will be performed in triplicate at screening. Patients should be in the semi-recumbent or supine position.

5.3. Zanubrutinib Dispensation

Zanubrutinib will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the Pharmacy Manual. Instructions are to be provided for dosing, storage, and the return of all bottles (used and unused) at future visits.

5.4. Pharmacokinetics

Blood samples to assess plasma zanubrutinib concentrations will be collected in patients in arm A. Sparse PK samples will be collected from patients randomized to arm A (zanubrutinib plus obinutuzumab) at the following time points: predose (within 30 min prior to zanubrutinib dose), and 2 hours (± 30 min) post zanubrutinib dose on Cycle 1 Day 1 and Cycle 2 Day 1. No sparse PK samples are required during crossover treatment. On the days PK samples are to be collected, study drug administration must occur under the supervision of the investigator (or designee) after the predose PK sample is obtained. The actual time (to the nearest minute) of zanubrutinib administration on the day prior to Cycle 1 Day 1 and Cycle 2 Day 1 must be recorded on the eCRF. Should a drug-drug interaction between zanubrutinib and a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the interaction.

Blood samples (2 mL) for PK analysis will be collected into EDTA collection tubes. Details concerning handling of the PK plasma samples, including labeling and shipping instructions will be provided in the laboratory manual for this study. PK samples will only be collected from sites that are able to adequately follow the sampling, handling and processing procedures outlined in the laboratory manual.

Samples will be shipped to the designated bioanalytical lab for quantification of plasma zanubrutinib concentrations using a validated method.

5.5. Safety Assessments

Physical Examination and Vital Signs

Physical examination, vital signs (sitting blood pressure, heart rate, and body temperature), and weight will be performed at each study visit. Height (cm) is determined at screening only.

A complete physical exam includes an assessment of systems per standard of care at the study site and as clinically indicated by symptoms.

Assessment of vital signs and a focused physical examination on Cycle 1 Day 1 may be skipped if performed within 7 prior days.

ECOG Performance Status

ECOG performance status will be assessed at the screening visit, each visit during study treatment, and at the safety follow-up visit. Appendix 4 will be used to assess performance status.

Concomitant Medications Review

Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 35 days before the first visit in Cycle 1 and since the prior study visit, thereafter.

Adverse Events Review

Record AEs that occurred during screening on the medical history case report form and in the patient's clinical record.

Collect non-serious AE information from the time of first dose of study drug through safety follow-up. Information on all SAEs (regardless of relatedness) will be collected from the time of signed informed consent through screen failure or safety follow-up. The AE reporting period is defined in Section 8.4.1.

All treatment-related AEs and SAEs will be followed until resolution or stabilization. The accepted regulatory definition for an AE is provided in Section 8.1.1. Important additional requirements for reporting SAEs are explained in Section 8.4.2.

5.6. Efficacy Assessments

Response will be assessed by independent central review and categorized per the Lugano Classification for NHL (Cheson et al 2014). The primary endpoint will be ORR based on independent central review. Investigators will assess response without knowledge of independent central review results. Response parameters will include assessment of lymphadenopathy, hepatomegaly and splenomegaly, blood lymphocyte count, bone marrow aspirate/biopsy, platelet count, hemoglobin level, and neutrophil count. In the event of a treatment delay, disease assessments are to continue per the Schedule of Assessments (Appendix 9).

For patients receiving zanubrutinib, refer to Appendix 2 regarding the assessment of disease progression during study drug holds.

Disease-Related Constitutional Symptoms

Disease-related constitutional symptoms (or B-symptoms) (unexplained fever of ≥ 101°F [or 38.3°C], drenching night sweats; or unexplained loss of > 10% body weight within the previous 6 months) will be evaluated at screening, every 12 weeks from Cycle 1 Day 1 for 24 months, then every 24 weeks for 24 months, and then yearly until disease progression.

Exam of Liver, Spleen and Lymph Nodes

Enlargement of liver, spleen, and lymph nodes is included in the physical examination at screening, every 12 weeks from Cycle 1 Day 1 for 24 months, then every 24 weeks for 24 months, and then yearly until disease progression.

Imaging Assessments

All patients must have baseline (within 35 days of randomization) PET/CT scan with contrast of neck, chest, abdomen, and pelvis and any other disease sites.

Patients with suspected transformation of disease (eg, a PET/CT with high standardized uptake value-avidity or new onset symptoms) should be fully evaluated prior to enrollment on study.

Screening findings will determine whether patients are followed with contrast-enhanced PET/CT or contrast-enhanced CT only. Patients with disease that is FDG-avid by either site assessment or the central imaging vendor must be followed by PET/CT.

Ideally, and depending on the imaging equipment available, contrast-enhanced CT should occur combined with PET on a single visit. Combined PET/CT may be used in lieu of a CT with contrast only if the CT of the combined PET/CT has been performed with diagnostic quality and contrast is administered.

PET/CT scans are required at screening and after Cycles 3, 6, and 12. A PET/CT scan is required to confirm a result on CT scan (CR/PR or disease progression).

CT with contrast will be performed at all other tumor assessment timepoints (see Appendix 9, Schedule of Assessments).

For patients with a contraindication to receiving CT scan IV-contrast (eg, contrast allergy, or other medical contraindication such as renal insufficiency), magnetic resonance imaging (MRI) may be used in place of CT scans. For patients being assessed via MRI, a non-contrast chest CT scan is acceptable, and preferred, in place of a chest MRI to evaluate the lung parenchyma. The same imaging technique (ie, CT, MRI) should be used consistently throughout a patient's time on the study. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a patient's remaining course on study.

All PET/CT scans, CT scans, and MRIs obtained during the study will be collected and reviewed by a central imaging vendor identified to this trial. De-identified copies of all scans and radiology reports (including those from screening) must be provided to the sponsor or designee (eg, central imaging vendor).

Modification from Lugano Classification for NHL (Cheson et al 2014):

Pseudoprogression is defined as an objective tumor response occurring after initial documentation of apparent radiological progressive disease and has been observed in patients receiving a BTK inhibitor for treatment of follicular lymphoma (Salles et al 2016). For patients in either arm, a timepoint finding of "disease progression" will require a confirmatory scan at least 4 weeks after the scan that initially demonstrated possible progression. An exception to the confirmatory scan requirement exists if one or more of the following clear, clinical signs of progression is present and the investigator believes the progression is unequivocal:

a. Clinical symptoms and signs of disease progression (including worsening laboratory values)
b. Deterioration of ECOG performance status
c. Rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that necessitates urgent medical intervention.

Note: If any of the conditions above are present, no confirmatory scan is required to confirm the disease progression.

Due to the potential for pseudoprogression cases in this study, patients in both Arms A and B should remain on study treatment while the patient waits for the confirmation scan results.

Bone Marrow Examination

Bone marrow biopsy is required under the following conditions during the treatment period: during screening to assess bone marrow involvement of lymphoma; and if clinical and laboratory results demonstrate that a CR has been achieved, in order to confirm a CR – only applicable to patients whose bone marrow was positive for lymphoma involvement at screening.

Bone marrow biopsies will be reviewed by local laboratory and results will be entered into the CRF. In addition, all of the bone marrow samples from screening to end of study will be collected to be reviewed by a pathologist from central pathology laboratory.

5.7. Patient-Reported Outcomes

PROs will continue to be assessed until disease progression, death, or withdrawal of consent, regardless of study treatment discontinuation. Patients should complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires per the Schedule of Assessments (Appendix 9) before study drug is administered, and when possible before performing any other procedures. No PRO questionnaires are required during crossover treatment.

EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (EuroQol Group 1990; Herdman et al, 2011). Patients will self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire also includes a visual analog scale to self-rate general health state on a scale from "the worst health you can imagine" to "the best health you can imagine." A sample questionnaire is provided in Appendix 6 as an example only.

EORTC QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is a copyrighted instrument, which has been translated and validated in over 100 languages and is used in more than 3,000 studies worldwide. The EORTC QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), 1 Global Health Status scale, 3 symptom scales (Fatigue, Nausea and Vomiting, and Pain), and 6 single items (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties) (Fayers et al, 2001). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients in general, and specifically in non-Hodgkin lymphoma patients. It is a reliable and valid measure of PRO in cancer patients and takes about 11 minutes to administer. A sample questionnaire is provided in Appendix 7 as an example only.

5.8. Laboratory Assessments

Samples for protocol-specified CBC, chemistry and coagulation profiles will be evaluated by a central laboratory. Additional laboratory assessments, including lab values required within a short timeframe on dosing days to determine drug dosage, and unscheduled laboratory tests

ordered by the investigator as necessary for patient monitoring, will be performed locally and entered into the eCRF. Samples for serum immunoglobulins, β_2-microglobulin, pregnancy testing, and hepatitis B and C testing will be performed locally. These tests may be performed centrally in certain countries.

A detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels is provided in the laboratory manual.

Chemistry, CBC with differential, coagulation, serum immunoglobulin, and β_2-microglobulin, will be performed at the timepoints specified in the Schedule of Assessment (Appendix 9), and may also be performed as medically necessary. On Cycle 1 Day 1, laboratory assessments should be done before the study drug administration. Screening blood and tests performed within 72 hours of the first study drug administration do not need to be repeated on Cycle 1 Day 1.

Hematology

CBC with differential is required to be performed at every visit during the treatment phase and during safety follow-up and long-term follow-up. CBC includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count with differential including neutrophils (including bands), lymphocytes, monocytes, eosinophils, and basophils.

Chemistry

Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase.

Serum Immunoglobulins

Quantitative serum immunoglobulins (IgG, IgM, IgA) will be measured at screening; on Day 1 of Cycle 3, Cycle 6, Cycle 9, and Cycle 12; and then every 24 weeks thereafter until disease progression.

Coagulation

The coagulation profile includes prothrombin time, which will also be reported as international normalized ratio, and activated partial thromboplastin time. The coagulation profile will be performed at screening only.

Hepatitis B and C testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening. The hepatitis B testing includes HBsAg, HBcAb, and hepatitis B surface antibody (HBsAb) as well as HBV DNA by PCR if the patient is negative for HBsAg, but HBcAb positive (regardless of HBsAb status). The hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is HCV antibody positive. Patients with positive HBsAg and/or detectable level of HBV DNA or detectable level of HCV RNA are not eligible.

Patients who are HBsAg-negative, HBcAb-positive and HBV DNA-negative must undergo at least monthly HBV DNA screening by PCR. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If, during monthly

monitoring of HBV DNA by PCR, the value is between 20 IU/mL and 100 IU/mL, then the HBV DNA level should be rechecked within 2 weeks. Study drug should be stopped and antiviral therapy initiated if the repeat level is between 20 IU/mL and 100 IU/mL. If the HBV DNA by PCR is 100 IU/mL or higher, then study drug should be stopped and antiviral therapy initiated or continued. Resumption of study drug in patients whose HBV reactivation resolves should be discussed with, and approved by, physicians with expertise in managing hepatitis B.

Patients positive for HCV antibody, but negative for HCV RNA, must undergo monthly HCV RNA screening. Patients with HCV RNA of 15 IU/mL or greater should stop study drug and antiviral therapy should be initiated. Resumption of study drug in patients whose HCV reactivation resolves should be discussed with, and approved by, physicians with expertise in managing hepatitis C.

The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

Table 1 below, shows how the results for, HBV/HCV, and HBV/HCV testing at screening relate to inclusion and exclusion criteria.

Table 1: Active Hepatitis B (HBV) or Hepatitis C (HCV) Infection (Detected Positive by PCR)

Screening Assessment	Meets Inclusion Criteria	To be Excluded
HBV	**HBsAg (-) and HBcAb (-)**	**HBsAg (+)**
	HBsAg (-) *and* HBcAb (+) *HBV DNA "Not detected"* *Perform monthly monitoring of HBV DNA	**HBsAg (-) *and* HBcAb (+)** *HBV DNA detected*
HCV	**Antibody (-) *or* Antibody (+)** *HCV RNA "Not detected"* *Perform monthly monitoring of HCV RNA	**Antibody (+)** *HCV RNA Detected*

Abbreviations: HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; HCV, hepatitis C virus.

Pregnancy Test

A serum pregnancy test will be performed at screening, within 7 days of randomization, and at the end of treatment in women of childbearing potential. During treatment, laboratory-based, highly-sensitive pregnancy tests (urine or serum) will be performed within 4 weeks after Cycle 1, Day 1, then every 4 weeks even if the timing falls outside of the normally scheduled visits. Pregnancy tests must be continued every 4 weeks for at least 90 days after the last dose of study drug (even if the timing falls outside of the normally scheduled visits). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. A patient who has a positive

pregnancy test result at any time after the study drug administration will be immediately withdrawn from treatment in the study.

5.9. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or investigator's request and may include vital signs/focused physical examination; ECOG performance status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; hematology and chemistry laboratory assessments; serum immunoglobulins; and pregnancy tests. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

5.10. Arm B "Crossover" Treatment Adding Zanubrutinib

At investigator discretion, and with medical monitor approval, patients in Arm B may "crossover" to add zanubrutinib following disease progression confirmed by independent central review. To initiate crossover therapy with zanubrutinib, a patient must meet the safety and laboratory test requirements documented below. Once approved for crossover, these patients will continue to follow the required safety and laboratory procedures in the Schedule of Assessments (Appendix 9) while receiving zanubrutinib and obinutuzumab. No sparse PK samples or PRO questionnaires are required during crossover treatment. The total duration of obinutuzumab treatment (ie, total of monotherapy plus combination therapy) will be approximately 30 months (maximum 20 doses). Following completion of 20 doses of obinutuzumab treatment, patients receiving crossover therapy will continue to receive zanubrutinib until disease progression. Tumor response will be evaluated by the investigator.

To request crossover treatment adding zanubrutinib, site staff will complete the Request for Crossover Treatment form and submit it to the medical monitor for approval following independent central review confirmation of disease progression. Documentation must be provided showing that the patient meets the following requirements within 15 days before date of submission of the form:

- ANC $\geq 1000/mm^3$, except when neutropenia is assessed by the investigator to be directly due to active lymphoma, in which case ANC must be $\geq 750/mm^3$
- Platelet $> 50{,}000/mm^3$ (without growth factor support or transfusion within 7 days)
- Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft-Gault or MDRD equation or as measured by nuclear medicine scan or 24-hour urine collection)
- AST/serum glutamic oxaloacetic transaminase, and (ALT)/serum glutamic pyruvic transaminase ≤ 3.0 x ULN
- Serum total bilirubin < 2.0 x ULN (unless documented Gilbert's syndrome)
- No known New York Heart Association Class III or IV congestive heart failure (see Appendix 4)

- QTcF ≤ 480 milliseconds based on Fridericia's formula

The investigator will confirm that the above crossover requirements are met and that the patient qualifies to add full dose zanubrutinib at 160 mg twice daily. Contact the medical monitor for any patient being considered for crossover who, based on the protocol dose modification section, would be required to implement a dose modification or a delay in the initial dosing of zanubrutinib.

Patients approved to receive crossover treatment with combination zanubrutinib plus obinutuzumab should begin zanubrutinib as soon as possible after crossover approval. If the timing of the crossover approval does not align with a visit for obinutuzumab administration, the patient should come to clinic for an unscheduled visit. The first crossover visit should include education about the combination therapy and the dose, route, and frequency of zanubrutinib administration; the patient should initiate zanubrutinib therapy on the date of the first crossover visit.

5.11. End of Treatment Period

The treatment period starts with the first day of assigned study treatment and includes ongoing assessments for safety and efficacy per the Schedule of Assessments following completion of protocol-specified treatment. The treatment period ends on the first day of next-line therapy or on the day of confirmed disease progression, whichever occurs first.

Patients may discontinue study drug for any one of the following reasons:

- Disease progression
- Any intolerable adverse event that cannot be improved with standard medical intervention or would lead to undue risk to the patient
- Patient withdrew consent
- Patient pregnancy
- Investigator decision
- Other

Patients may voluntarily withdraw consent from treatment at any time.

5.12. Safety Follow-Up

All patients who permanently discontinue zanubrutinib will have a safety follow-up visit 30 (± 7) days after the last dose of study drug to collect AEs, including AEs that may have occurred or been ongoing after the patient discontinued study treatment. For the obinutuzumab monotherapy arm (Arm B), the safety follow-up visit will occur 90 days after the last dose of study drug. The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. A laboratory assessment is only required if the patient had an ongoing laboratory abnormality at the previous visit that the investigator considered to be related to study drug. If the patient is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the

patient or guardian to collect this information. Refer to the Schedule of Assessments (Appendix 9) for the assessments to be performed at the safety follow-up visit.

5.13. Long-Term Follow-Up

All patients who discontinue study drug treatment will remain in the study, complete safety follow-up, and subsequently commence long-term follow-up, which includes monitoring survival status and subsequent therapies for follicular lymphoma, and which may also include imaging and tumor response assessments for patients who have not yet had confirmed radiographic progression. Visits repeat every 12 weeks (± 14 days) until study end. For patients who permanently discontinue study drug treatment before radiographic progression is documented and confirmed by independent central review, tumor assessments (including radiographic imaging) will continue until radiographic progression is identified and confirmed by independent central review or start of next-line therapy, whichever comes first. Patients with centrally confirmed disease progression will be followed up only for survival status and information about their next-line therapy.

If the patient refuses to return for these visits or is unable to do so, every effort should be made to contact them or patient's guardian by telephone to determine the patient's disease status and survival.

5.14. End of Study

Reasons for complete withdrawal from the study (including treatment and all follow-up visits) will occur under the following circumstances:

- Patient withdrew consent
- Death
- Study termination by sponsor
- Other

Patients may voluntarily withdraw consent from the study at any time.

5.15. Lost to Follow-Up

Every reasonable effort should be made to contact any patient apparently lost to follow up during the study to complete study related assessments, record outstanding data, and retrieve study drug.

Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives). Such efforts should be documented in the patient's source documents.

If all efforts fail to establish contact, the patient will be considered lost to follow up.

6. STUDY TREATMENT

6.1. Study Treatment Preparation and Dispensation

6.1.1. Packaging and Labeling

Zanubrutinib capsules will be provided in a child-resistant high-density polyethylene bottle with an induction seal and bottle label. Obinutuzumab will be provided in vials containing solution for infusion.

The contents of the label will be in accordance with all applicable local regulatory requirements.

6.1.2. Handling and Storage

The IRT system will be used for drug supply management. The study drugs will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledgment receipt of all study drug shipments. All study drugs must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with study drug-specific requirements. The study drugs must be kept at the temperature condition as specified on the labels.

Zanubrutinib bottles must be stored at room temperature 15ºC to 30ºC.

Obinutuzumab must be stored at 2°C to 8°C (36°F to 46°F), protected from light and should not be frozen or shaken. For the diluted product, chemical and physical stability have been demonstrated in 0.9% NaCl at concentrations of 0.4 mg/mL to 20 mg/mL for 24 hours at 2°C to 8°C (36°F to 46°F) followed by 48 hours (including infusion time) at room temperature (≤ 30°C/86°F). The solution for infusion should be used immediately. If not used immediately, the prepared solution may be stored up to 24 hours at 2°C to 8°C.

Study drugs must be dispensed or administered according to procedures described herein. Only patients enrolled in the study may receive study drug(s), in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug(s).

6.1.3. Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or guardian.

The investigator and/or study personnel will keep accurate records of the quantities of study drug dispensed and used by each patient. This information must be captured in the source document at each patient visit. The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor, the amount supplied, and/or administered to and returned by patients, if applicable.

6.1.4. Disposal and Destruction

After completion of the study, and following final drug inventory reconciliation by the monitor, the study site will destroy or return all unused study drug supplies. The inventoried supplies can be destroyed on site or at the depot according to institutional policies, after receiving written sponsor approval.

6.2. Dosage and Administration

6.2.1. Zanubrutinib

Zanubrutinib will be dispensed by the study center personnel to patients at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the Pharmacy Manual. The investigator is to instruct the patient to take the study drug exactly as prescribed and at the same time each day of dosing. Patients will be requested to bring their unused medication and all empty bottles to the center at each visit. All dosages prescribed and dispensed to the patient and all dose changes including reason for dose changes during the study must be recorded on the appropriate eCRF.

Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients will take zanubrutinib with water at approximately the same time every day, with a minimum of 8 hours between consecutive doses. Zanubrutinib capsules should not be opened, broken, or chewed at any time.

Patients receiving zanubrutinib should be instructed that if a dose of the study drug is not taken at the scheduled time, they should skip the study drug if the time to next dose is 8 hours or less, and return to normal dosing with next dose. If a patient vomits after taking the zanubrutinib capsules, that dose should not be repeated.

On the days of PK blood sampling, study drug administration for patients assigned to arm A (zanubrutinib plus obinutuzumab) will occur at the center after the predose blood sampling has occurred under the supervision of the investigator or his/her designee. The investigator or his/her designee must instruct the patient not to self-administer the study drug prior to the office visit on those days.

6.2.2. Obinutuzumab

Patients will receive obinutuzumab 1,000 mg intravenously on days 1, 8, and 15 of Cycle 1, then 1,000 mg on Day 1 of Cycles 2 to 6, then 1,000 mg every 8 weeks. (At the discretion of the investigator, obinutuzumab may be administered 100 mg on Day 1 and 900 mg on Day 2 of Cycle 1 instead of 1,000 mg on Day 1 of Cycle 1.) Responding patients may continue to receive maintenance obinutuzumab every 8 weeks for an additional 24 months (eg, maximum total duration of obinutuzumab of approximately 30 months [maximum 20 doses]).

Obinutuzumab should be administered at a rate of 50 mg/hr. The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If no infusion reaction occurs during the Cycle 1 Day 1 infusion and the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr for all subsequent doses. Patients should be

premedicated with acetaminophen, antihistamine, and a glucocorticoid before each obinutuzumab infusion.

6.3. Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any AE or SAE criterion must be reported in the appropriate timeframe as an AE or SAE. There is no specific antidote for zanubrutinib. In the event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

There has been no experience with overdose in obinutuzumab. Doses ranging from 50 mg up to and including 2000 mg per infusion have been administered in clinical trials. For patients who experience overdose, treatment should consist of immediate interruption or reduction of obinutuzumab and supportive therapy.

6.4. Precautions

6.4.1. Surgery and Procedures

Susceptibility to bleeding has been observed with BTK inhibitors. Study treatment with zanubrutinib should be held for 3 to 7 days before and after surgery, depending upon the type of surgery and the risk of bleeding. Obinutuzumab should also be interrupted, if applicable.

6.5. Dose Interruption and Modification

The guidelines set forth in Table 2 should be followed for dose interruption or modification of zanubrutinib for hematologic (Section 6.5.1) or nonhematologic (Section 6.5.2) toxicities. No dose modifications for obinutuzumab are allowed.

Temporary drug holds may cause short term worsening of disease. Please review note at the end of Appendix 2 when assessing disease after a drug hold.

Table 2: Zanubrutinib Dose Reduction Steps

Dose Level	Zanubrutinib Dose (Arm A)
0 = starting dose	160 mg twice a day
-1 dose level	80 mg twice a day
-2 dose level	80 mg once a day

Zanubrutinib may be restarted upon resolution of toxicity and per investigator discretion if held for ≤ 28 consecutive days. If, in the investigator's opinion, it is in the patient's best interest to restart treatment after > 28 days, then written approval must be obtained from the sponsor's medical monitor.

6.5.1. Zanubrutinib Dose Reductions for Hematologic Toxicity

Dosing will be held for individual patients under any of the following conditions, based on investigator assessment of study drug relatedness:

- Grade 4 neutropenia (lasting > 10 days)
- Grade 4 thrombocytopenia (lasting > 10 days)
- Grade 3 thrombocytopenia associated with significant bleeding
- ≥ Grade 3 febrile neutropenia

For the first occurrence of hematologic toxicity, treatment may restart at full dose upon recovery of the toxicity to ≤ Grade 1 or baseline.

If the same event reoccurs, subjects will restart at one dose level lower upon recovery of the toxicity to ≤ Grade 1 or baseline.

A maximum of 2 dose reductions will be allowed.

Subjects with Grade ≥ 3 thrombocytopenia associated with significant bleeding requiring medical intervention should be discussed with the medical monitor.

6.5.2. Zanubrutinib Dose Reductions for Nonhematologic Toxicity

For nonhematological toxicities ≥ Grade 3 (other than atrial fibrillation, or hypertension adequately controlled with oral medication) or asymptomatic laboratory events (laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events), suspected to be related to study drug treatment, study drug will be held until recovery to ≤ Grade 1, and then restarted at original dose level. If the event recurs at ≥ Grade 3, drug will be held until recovery to ≤ Grade 1 and restarted at level -2. If the event recurs at ≥ Grade 3 at level -2, the patient will be discontinued from study treatment.

For patients experiencing atrial fibrillation that is symptomatic and/or incompletely controlled: after the atrial fibrillation is adequately controlled study drug may be restarted at either the original dose or dose level -1, per discretion of the treating investigator.

Zanubrutinib should be permanently discontinued for any intracranial hemorrhage.

For information on study drug holds based on the results of hepatitis B or hepatitis C testing, see Section 5.8.

6.5.3. Dose Interruptions and Modifications for Obinutuzumab

There are no dose modifications of obinutuzumab.

Obinutuzumab can cause severe and life-threatening infusion reactions. Stop obinutuzumab infusion immediately and permanently discontinue for Grade 4 infusion reactions. Interrupt obinutuzumab infusion and manage symptoms for Grade 3 infusion reactions; upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if the patient does not experience any further infusion reaction symptoms, the infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose. Permanently

discontinue obinutuzumab treatment if patients experience a Grade 3 infusion-related symptom at rechallenge. For Grade 1 or 2 infusion reactions, reduce infusion rate or interrupt infusion and treat symptoms; upon resolution of symptoms, continue or resume infusion and, if the patient does not experience any further infusion reaction symptoms, the infusion rate escalation may be resumed at the increments and intervals as appropriate for the treatment cycle dose.

Consider obinutuzumab treatment interruption if patients experience an infection, Grade 3 or 4 cytopenia, or a ≥ Grade 2 nonhematologic toxicity. Refer to the obinutuzumab Investigator Brochure or local prescribing information (if available), for guidance regarding infusion reactions, as well as for dose withholding or discontinuation in response to specific toxicities associated with obinutuzumab.

7. PRIOR AND CONCOMITANT THERAPY

7.1. Prior Therapy

Medications taken within 4 weeks before randomization and any medications prescribed for chronic or intermittent use during the study, or dose adjustments of these medications, will be recorded on the eCRF and in the patient's source documents.

All prior therapies for follicular lymphoma, including immunochemotherapy, chemotherapy, transplant, targeted therapy, radiation therapy, etc. will be recorded on the eCRF with the dates of administration.

Per the study eligibility criteria, patients who received prior certain medications and therapies for follicular lymphoma (including allogeneic hematopoietic stem cell transplantation within 12 months of study enrollment and prior exposure to a BTK inhibitor) are excluded from study participation.

7.2. Concomitant Therapy

All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information, and dates of administration.

Patients with high tumor burden should be monitored closely and prophylactic measures, including allopurinol or rasburicase, may be instituted per institutional standards.

Prophylactic measures against infection, for the prevention of bacterial or fungal infections and/or for the prevention of hepatitis B infection reactivation, may be used per institutional standards.

Patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are pre-disposed to opportunistic infections as a result of disease and treatment-related factors. In patients with a high risk for opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), prophylaxis should be considered as per institutional standards.

7.2.1. Permitted Medications

The following treatments are allowed:

- Blood transfusions and growth factor support per standard of care and institutional guidelines
- Corticosteroids for non-follicular lymphoma indications

  Patients should not receive treatment with systemic corticosteroids other than intermittently to control or prevent infusion reactions, or for short durations (< 2 weeks) to treat non-follicular lymphoma-related conditions (eg, to treat a flare of chronic obstructive pulmonary disease), or at doses less than 20 mg/day of prednisone or prednisone-equivalent given daily to treat non-follicular lymphoma-related conditions

- Therapy to reduce symptoms of disease per standard of care and institutional guidelines

Tumor lysis syndrome has not been currently reported with zanubrutinib treatment, but has been reported rarely with obinutuzumab. Patients with high tumor burden should be monitored closely and prophylactic measures, including allopurinol, may be instituted per institutional standards.

7.2.2. Prohibited Medications

Patients should not receive other anticancer therapy (cytotoxic, biologic, or immunotherapy) while on treatment in this study. Other anticancer therapy should not be administered until disease progression (as per clinical practice standards at the study center), unmanageable toxicity, or no further clinical benefit occurs which requires permanent discontinuation of the study drug.

7.3. Potential Interactions Between the Study Drugs and Concomitant Medications

7.3.1. CYP-Inhibiting/Inducing Drugs

When administering zanubrutinib, caution should be used with the any of the following, because they may affect the metabolism of zanubrutinib:

- Strong/moderate CYP3A inhibitors
- CYP3A inducers
- Grapefruit juice
- Seville oranges

If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. However, if CYP3A inhibitors or inducers will be used, follow the dose modification table in Appendix 8. The medical monitor should be consulted in these situations. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

A clinical drug-drug interaction study indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19. Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs. Since blood levels and effectiveness of drugs that are substrates for CYP3A (eg, steroidal contraceptives) may be reduced by CYP3A inducers, if patients are using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must be used. The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.

No formal drug interaction studies have been conducted with obinutuzumab (GAZYVA package insert).

8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

8.1. Adverse Events

8.1.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In these instances, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

8.1.1.1. Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v4.03.

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

NOTE: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.4.2.

8.1.1.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or Prescribing Information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes an assessment of causality for every SAE prior to transmission of the SAE report to the sponsor since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related". An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered 'related' to study drug if any of the following are met, otherwise the event should be assessed as not related:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely

- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.1.1.3. Follow-Up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient withdraws consent. Any changes in the severity of AEs/SAEs, must be recorded in the appropriate AE or SAE eCRF page(s); both increases in grade and decreases in grade will be recorded with updated start and stop dates. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE report, with all changes signed and dated by the investigator. The updated SAE report should be resent to the sponsor within the timeframes outlined in Section 8.4.2.

8.1.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, CBC, or coagulation) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. However, clinically significant abnormal laboratory findings or other abnormal assessments that are present at the start of the study and do not worsen will not be reported as AEs or SAEs. The definition of clinically significant is left to the judgment of the investigator; in general, these are events that result in clinical signs or symptoms that require active medical intervention, or lead to dose interruption or discontinuation.

8.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

NOTE: the term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

  NOTE: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

- Results in disability/incapacity

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

8.3. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Investigator's Brochure.

8.4. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.4.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

For patients receiving zanubrutinib plus obinutuzumab: all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last dose of zanubrutinib, 90 days after the last dose of obinutuzumab.

For patients receiving obinutuzumab monotherapy: all AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after the last dose of obinutuzumab.

For patients who have the addition of zanubrutinib to obinutuzumab at 12 months, AEs will continue to be reported until 30 days after the last dose of zanubrutinib, 90 days after the last dose of obinutuzumab.

After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.

8.4.2. Reporting Serious Adverse Events

8.4.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be be reported promptly to the sponsor or designee as described in Table 3.

Table 3: Timeframe and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

Type	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report form	As expeditiously as possible	SAE report form	Email or fax SAE report form

Abbreviation: SAE, serious adverse event.

8.4.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours as outlined above in Section 8.4.2.1. The SAE report will always be completed as thoroughly as possible with all available details of the SAE and forwarded to the sponsor or designee within the designated timeframes.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the sponsor of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality for each SAE as described in Section 8.1.1.2.

The sponsor will provide contact information for SAE receipt.

8.4.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.4.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

This protocol is being filed under an Investigational New Drug (IND) protocol amendment with the United States FDA. Once active, a given SAE may qualify as an IND safety report if the SAE is both attributable to the study drug and unexpected. In this case, all investigators filed to the IND (and associated INDs for the same compound) will receive an expedited investigator safety report, identical in content to the IND safety report submitted to the FDA.

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. The purpose of the report is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

When a study center receives an initial or follow-up report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

8.4.3. Eliciting Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

8.4.4. Disease Progression

Disease progression (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the AE term(s).

For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion due to disease progression" instead of "disease progression". If a patient experienced a fatal multi-organ failure due to disease progression, the term "multi-organ failure due to disease progression" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression."

8.4.5. Deaths

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg “death”, “death of unknown cause”, or “death unexplained.”

8.4.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving study treatment or within 90 days of the last dose of study drug, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

8.5. Post-Study Adverse Event

A post-study AE or SAE is defined as any adverse event that occurs after the AE/SAE reporting period, defined in Section 8.4.1.

Investigators are not obligated to actively seek AEs or SAEs in former patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the SAE related to the study drug, the investigator will notify the sponsor.

8.6. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards and Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs and IECs based on applicable legislation.

To determine the reporting requirements for individual serious adverse events, the sponsor will assess the expectedness of the SAEs using the following reference documents:

- BeiGene Investigator Brochure BGB-3111
- Obinutuzumab Investigator Brochure and/or Prescribing Information (for marketed products)

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.1. Study Endpoints

9.1.1. Primary Endpoint

The primary endpoint is overall response rate determined by independent central review using Lugano Classification for NHL (modified from Cheson et al, 2014). The overall response rate is defined as the proportion of patients who achieve either complete response or partial response as best overall response. Best overall response is defined as best response achieved during the entire follow-up period. However, for the patients in arm B who cross over to arm A, the disease assessment after the crossover will not be included in the derivation of best overall response.

9.1.2. Secondary Endpoints

- Overall response rate determined by investigator assessment
- Duration of response determined by independent central review and by investigator assessment, defined as the time from the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever occurs first
- Progression-free survival determined by independent central review and by investigator assessment, defined as the time from randomization to the date of first documentation of disease progression or death, whichever occurs first
- Overall survival defined as the time from randomization to the date of death due to any reason.
- Rate of complete response or complete metabolic rate determined by independent central review and by investigator assessment, defined as the proportion of patients who achieve complete response or complete metabolic rate as best overall response
- Time-to-response determined by independent central review and by investigator assessment, defined as the time from randomization to the time the response criteria are first met
- Patient-reported outcomes measured by EORTC QLQ-C30 and EQ-5D-5L questionnaires
- Safety parameters, including AEs, SAEs, clinical laboratory tests, physical exams, and vital signs
- PK parameters such as apparent clearance of the drug from plasma (CL/F) and AUC_{0-12}

9.1.3. Exploratory Endpoint

- Overall response rate in arm B after crossover to arm A.

9.2. Statistical Analysis

9.2.1. Randomization Methods

As discussed in Section 5.1, patients will be randomized using the IRT system for this study by permuted block stratified randomization using the number of prior lines of therapy (2 to 3 vs > 3), rituximab-refractory status (yes vs no), and geographic region (China vs ex-China) as strata.

9.2.2. Analysis Sets

The Intent-to-Treat (ITT) analysis set includes all enrolled patients who are randomized. The ITT analysis set will be the primary population used for efficacy analyses.

The Safety analysis set includes all patients who received any dose of study drug. Patients will be included in the treatment groups corresponding to the actual treatment received. The Safety analysis set will be used for all safety analyses.

The Per-Protocol analysis set includes patients who received any dose of study drug and had no major protocol deviations. Criteria for exclusion from the Per-Protocol analysis set will be determined and documented before the database lock for the primary analysis.

The PK analysis set includes all zanubrutinib-treated patients who have at least one measurable PK concentration.

9.2.3. Efficacy Analysis

9.2.3.1. Primary Efficacy Endpoint Analysis

Primary inference of comparing overall response rate by independent central review will be based on a Cochran-Mantel-Haenszel test adjusted for the randomization factors (number of prior lines of therapy [2 to 3 vs > 3], rituximab-refractory status [yes vs no]), and geographic region (China vs ex-China) in the ITT analysis set.

The null and alternative hypotheses for comparing overall response rate are as follows:

H_0: $ORR_A = ORR_B$

Ha: $ORR_A > ORR_B$

where ORR_A is the overall response rate in arm A (zanubrutinib plus obinutuzumab) and ORR_B is the overall response rate in arm B (obinutuzumab monotherapy). If the obtained one-sided p-value is ≤ 0.025, it will be concluded that the combination therapy of zanubrutinib plus obinutuzumab results in a statistically significantly increase in ORR versus obinutuzumab monotherapy; thereby demonstrating the superiority of arm A over arm B.

A common response rate difference (ORR_A - ORR_B) will be estimated using Cochran-Mantel-Haenszel weights based on the number of patients in each stratum with 95% stratified confidence interval (CI). The common odds ratio of overall response rate and its 2-sided 95%

CIs will be calculated. A Clopper-Pearson 95% CI of overall response rate will be constructed per each arm.

Best overall response will be defined as the best response recorded from randomization till data cut or start of new anticancer treatment. The disease assessments after crossover for patients in arm B who cross over to arm A will not be included in the determination of best overall response. Patients with no post-baseline response assessment (due to whatever reason) will be considered as non-responders. The proportion for each of the best response categories, complete response and partial response, will be presented by treatment group.

The data cutoff for the primary efficacy analysis will be approximately 3 months after randomization of the last patient. Study follow-up will continue as described in Section 3.4, Section 5.13, and Section 8.4.

Additional analysis details will be provided in the SAP.

9.2.3.2. Secondary Efficacy Endpoint Analyses

Duration of Response

Duration of response will be summarized only for patients who have achieved an objective response. The distribution of duration of response will be summarized for each treatment group by the Kaplan-Meier method.

Progression-free Survival

PFS will be compared based on the log-rank test stratified by the randomization stratification factors (number of prior lines of therapy [2 to 3 vs > 3], rituximab-refractory status [yes vs no], and geographic region [China vs ex-China]). The distribution of PFS, including median PFS and PFS rate at selected timepoints, will be estimated using the Kaplan-Meier method for each arm.

The censoring rules for PFS will follow United States FDA Guidance for Industry, *Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics* (2007) as follows.

- PFS for patients without any post-baseline disease assessment will be censored at the time of randomization
- PFS for patients without disease progression or death at the time of analysis will be censored at the time of the last disease assessment
- PFS for patients who are lost to follow-up prior to documented disease progression will be censored at the last disease assessment date
- PFS for patients who start to receive new anticancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy
- PFS for patients with disease progression or death occurring immediately after two or more missed consecutive disease assessments will be censored at the last assessment tumor assessment before the missed consecutive disease assessments

Overall Survival

OS between the 2 treatment groups will be compared using the same methods employed for the PFS comparison. The distribution of OS (including median and other quartiles) and OS rate at selected timepoints will be estimated by the Kaplan-Meier method.

Complete Response/Complete Metabolic Response

CR rate and complete metabolic response rate will be calculated as the proportion of patients who reached best overall response of CR (complete metabolic response) or higher. The CR and complete metabolic response rate will be compared between treatment groups using Fisher's exact test. A Clopper-Pearson 95% CI of complete response rate and complete metabolic response rate will be constructed per each arm.

Time-to-Response

Time-to-response will be summarized only for responders by sample mean, median and standard deviation for each treatment group.

Patient-Reported Outcomes

The EORTC QLQ-C30 questionnaire will be summarized for each assessment timepoint. The percentage of patients with a clinically meaningful change from baseline in 'global health status/QOL' and functional domains will be summarized as "improved", "stable" or "worsened" and compared between arms A and B. The data will also be analyzed using repeated measure mixed model to account for missing data under missing at random assumption.

Change of EQ-5D-5L score will be summarized descriptively.

9.2.3.3. Exploratory Efficacy Endpoint Analysis

The overall response rate in arm B after crossover to arm A will be summarized descriptively. An exact 95% CI will be provided.

9.2.3.4. Sensitivity Analysis

A subgroup analysis for ORR by independent central review and selected secondary endpoints will be performed.

Primary and selected secondary endpoints may be analyzed using the Per-Protocol analysis set as sensitivity analyses.

Time to event analysis for duration of response and time to response, which includes all patients, may be performed.

A multiple logistic regression will be performed in order to explore the relationship between the baseline prognostic factors and ORR, as well as to estimate the treatment effect adjusted for the imbalances in those factors.

9.2.4. Pharmacokinetic Analyses

Plasma zanubrutinib concentrations will be summarized by scheduled time of collection. A population PK analysis may be performed to include plasma concentrations of zanubrutinib from

this trial in an existing model. PK parameters such as apparent clearance of the drug from plasma and AUC_{0-12} may be derived from the population PK analysis if supported by data.

An exposure-response (efficacy or safety endpoints) analysis may be performed if supported by data. The results from the population PK and exposure-response analyses may be reported separately from the Clinical Study Report.

9.3. Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v4.03. Laboratory values (CBC, clinical chemistry, coagulation), vital signs, physical exams and electrocardiogram findings will also be used in determining the safety. Descriptive statistics will be used to analyze all safety data by treatment group.

9.3.1. Extent of Exposure

Extent of exposure to study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity (mg/day) and relative dose intensity.

The number (percentage) of patients requiring dose reductions, dose interruption, dose delay, and drug discontinuation due to AEs will be summarized. The cycle in which the first dose reduction/interruption occurred will be summarized using descriptive statistics. Frequency of reductions and dose interruptions will be summarized by categories.

Patient data listings will be provided for all dosing records and for calculated summary statistics.

9.3.2. Adverse Events

The AE verbatim descriptions (as recorded by the investigator on the eCRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA®). AEs will be coded to MedDRA (Version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term and primary system organ class are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy, whichever comes first. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of treatment-emergent AEs will be reported as the number (percentage) of patients with treatment-emergent AEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade according to NCI-CTCAE v.4.03 within a system organ class and preferred term, even if the patient experienced more than 1 treatment-emergent AE within a specific system organ class and preferred term. The number (percentage) of patients with treatment-emergent AEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to study drug or with missing assessment of the causal relationship. SAEs, deaths,

treatment-emergent AEs ≥ Grade 3, related treatment-emergent AEs, and treatment-emergent AEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

Incidence and time to diarrhea (≥ Grade 3), severe bleeding (defined as ≥ Grade 3 bleeding of any site or central nervous system bleeding of any grade), and atrial fibrillation will be summarized.

9.3.3. Laboratory Analyses

CBC and serum chemistry values will be evaluated for each laboratory parameter by treatment group. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the Clinical Study Report. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post-baseline visit.

Laboratory parameters that are graded in NCI-CTCAE (v.4.03) will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, heart rate, temperature, and weight) and changes from baseline will be presented by visit and treatment group for all visits. Vital signs will be listed by patient and visit.

9.3.5. Electrocardiogram

ECG assessments will be performed at the screening visit. Descriptive statistics for baseline ECG parameters will be presented.

9.3.6. Sample Size Considerations

The sample size calculation is based on the comparison of the primary endpoint of ORR in the ITT analysis set. Assuming $ORR_A = 0.55$ and $ORR_B = 0.30$, 210 patients will be enrolled in a 2:1 ratio (140 patients in arm A and 70 patients in arm B) to provide a power of approximately 91% in testing ORR_A versus ORR_B using a normal approximation to binomial distribution with a 2-sided significance level of 0.05 with continuity correction. The sample size calculation is based on methods in Hulley et al, 2013 and Fleiss et al, 1980.

9.3.7. Interim Analysis

There is no interim analysis planned for this study.

9.3.8. Final Analysis

A final analysis prior to study termination will be performed. The time and scope of the final analysis will be included in the SAP.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Steering Committee

This study will be overseen by a Steering Committee consisting of experts in follicular lymphoma and members of the sponsor's staff. The Steering Committee plays a central role in the design of the study, oversees the conduct of the study, and is to agree on a plan for communication of the results.

10.2. Data Monitoring Committee

An independent DMC consisting of experts in follicular lymphoma, clinical trial safety monitoring, and statistics will evaluate safety data periodically for this study. Approximately every 6 months after the first 50 patients are enrolled and have 3 months' follow-up, the DMC will review all available safety data. A separate charter will outline the details for the composition and responsibility of the DMC.

10.3. Independent Central Review

The sponsor will contract with an independent central review facility to provide an independent and blinded review of imaging and clinical data necessary to assess tumor response in the BGB-3111-212 study. This will be conducted by qualified, board-certified radiologists and hematologists assigned to the BGB-3111-212 study. An independent central review charter will describe the independent review and define the processes, roles, and responsibilities of the sponsor, the sites, the independent central review facility, and the reviewers.

10.4. Provision of Study Results and Information to Investigators

When the clinical study report is completed, the sponsor will provide the major findings of the study to the investigator.

In addition, details of the study drug assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her patient(s).

The sponsor will not routinely inform the investigator or patient of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

11. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

11.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

11.2. Investigator Responsibilities

11.2.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" International Conference for Harmonisation (ICH) guidelines, and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, and 21 CFR, Part 56, are adhered to.

11.2.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, the current version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the study center's informed consent form, and any other information that will be presented to potential patients (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before the study drug(s) can be shipped to the study center, the sponsor or its authorized representative must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential patients.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before new patients can consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the sponsor promptly.

11.2.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The

investigator must utilize an IRB/IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

Informed consent will be obtained before the patient can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

11.2.4. Investigator Reporting Requirements

As indicated in Section 8.4.2.3, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

11.2.5. Confidentiality

Information on maintaining patient confidentiality in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the informed consent form process, either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the trial.

The investigator agrees that all information received from BeiGene, including but not limited to the IB, this protocol, CRFs, the investigational drug, and any other study information, remain the sole and exclusive property of BeiGene during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from BeiGene. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.2.6. Case Report Forms

For each patient randomized/assigned to treatment, an eCRF must be completed and signed by the principal investigator or subinvestigator within a reasonable time period after data collection. If a patient withdraws from the study, the reason must be noted in the appropriate eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The eCRF exists within an electronic data capture (EDC) system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and applications of electronic signatures before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system,

with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRF is true by providing an electronic signature within the EDC system. After final database lock, the investigator will receive a copy of the patient data from that site (eg, paper, CD, or other appropriate media) for archiving the data at the study site.

11.2.7. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records and returned or destroyed study product. Dispensation records will document quantities received from BeiGene and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

11.2.8. Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

11.2.9. Protocol Adherence

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations.

11.3. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented.

Information on any change in risk and /or change in scope must be provided to patients already actively participating in the study, and they must read, understand and sign each revised ICF confirming willingness to remain in the trial.

11.4. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the sponsor and are confidential. Because this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors, 2013).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

11.5. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Resolve and close all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

11.6. Records Retention and Study Files

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, electrocardiogram, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples remaining after this study may be retained in storage by the sponsor for a period up to 2 years.

11.7. Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) is the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information which is necessary to disclose in order to provide appropriate medical care to a patient
- Study results which may be published as described in Section 11.4.

If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

11.8. Joint Investigator/Sponsor Responsibilities

11.8.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.8.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12. REFERENCES

Bachy E, Houot R, Morschhauser F, et al. Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. Haematologica. 2013;98(7):1107-14.

BeiGene Investigator Brochure, BGB-3111. Edition 4, February 2017.

Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. J Clin Oncol. 2015;33(23):2516-22.

Cheson B, Fisher R, Barrington S, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano Classification. 2014; J Clin Oncol. 2014;32:3059-67.

Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v83-90..

EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

Fayers PM, Aaronson NK, Bjordal K, et al, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels. 2001.

Fleiss JL, Tytun A, Ury HK. A simple approximation for calculating sample sizes for comparing independent proportions. Biometrics. 1980;36:343-46.

Food and Drug Administration Center for Drug Evaluation Research (CDER) and Center for Biologics Evaluation and Research. FDA guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. 2007.

Gazyvaro [prescribing information]. Grenzach-Wyhlen, Germany: Roche; 2016.

Gopal AK, Schuster SJ, Fowler N et al. Ibrutinib as treatment for chemoimmunotherapy-resistant patients with follicular lymphoma: first results from the open-label, multicenter, phase 2 DAWN study. Presented at the 58th American Society of Hematology (ASH) Annual Meeting. December 3-6, 2016; San Diego, CA. Abstract 1217.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727-36.

Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. J Clin Oncol. 2007;25(15):1986-92.

Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of CHOP significantly improves the outcome of patients with advanced stage FL compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005;106(12):3725-32.

Howlader N, Morton LM, Feuer EJ, et al. Contributions of Subtypes of Non-Hodgkin Lymphoma to Mortality Trends. Cancer Epidemiol Biomarkers Prev. 2016;25(1):174-9.

Hulley SB, Cummings SR, Browner WS, et al. Designing clinical research: an epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. Appendix 6B, page 75.

International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Updated August 2013. http://www.icmje.org.

Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program. 2009:523-31.

Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized phase 3 GALLIUM study. Presented at the 2016 ASH Annual Meeting, December 4, 2016; San Diego, California. Abstract 6.

Mounier M, Bossard N, Remontet L, et al. Changes in dynamics of excess mortality rates and net survival after diagnosis of follicular lymphoma or diffuse large B-cell lymphoma: comparison between European population-based data (EUROCARE-5). Lancet Haematol. 2015;2(11):e481-91.

National Comprehensive Cancer Network Treatment Practice Guidelines B-cell Lymphoma Version 3.2017: March 27, 2017.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Relander T, Johnson NA, Farinha P, et al. Prognostic factors in follicular lymphoma. J Clin Oncol. 2010;28(17):2902-13.

Salles GA, Trotman J, Lill M, et al. Pseudo-progression among patients with follicular lymphoma treated with ibrutinib in the phase 2 DAWN study. Blood. 2016;128:2980.

Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2007;99(9):706-14.

Sehn LH, Assouline SE, Stewart DA, et al. A phase 1 study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive B-cell malignancies. Blood. 2012;119(22):5118-25.

Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA101) with rituximab in patients with relapsed CD20 indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS study. J Clin Oncol. 2015;33(30):3467-74.

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016;17(8):1081-93.

Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004;104:1258-65.

Swerdlow S, Campo E, Harris NL, et al. WHO classification of tumors of hematopoetic and lymphoid tissues. IARC, Lyon. 2008.

Tam C, Grigg AP, Opat S, et al. The BTK inhibitor, Bgb-3111, is safe, tolerable, and highly active in patients with relapsed/ refractory B-cell malignancies: initial report of a phase 1 first-in-human trial. Blood. 2015;126:832.

Tam CS, Simpson D, Opat S, et al. Safety and activity of the highly specific BTK inhibitor BGB-3111 in patients with indolent and aggressive non Hodgkin's lymphoma (59th ASH Annual Meeting & Exposition oral presentation, Abstract #152). Blood 2017;130:152.

Zydelig FDA Alerts. March 14, 2016. https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-healthcare-professionals-about-clinical-trials-zydelig-idelalisib-combination-other. Accessed 11 August 2021.

Zydelig [prescribing information]. Foster City, CA: Gliead Sciences, Inc; 2016.

Zydelig [summary of product characteristics]. Foster City, CA: Gliead Sciences, Inc; 2016.

APPENDIX 1. SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: An International, Phase 2, Open-Label, Randomized Study of BGB-3111 Combined with Obinutuzumab Compared With Obinutuzumab Monotherapy in Relapsed/Refractory Follicular Lymphoma

PROTOCOL NO: BGB-3111-212

This protocol is a confidential communication of BeiGene, Ltd. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to PRA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

APPENDIX 2. MODIFIED LUGANO CLASSIFICATION FOR NHL

Response and Site	PET-CT-Based Response (Patients with FDG-Avid Disease at Screening)	CT-Based Response (Patients Without FDG-Avid Disease at Screening)
Complete	Complete metabolic response	Complete radiologic response (all of the following):
Lymph nodes and extralymphatic sites	Score 1, 2, 3* with or without a residual mass on 5-point scale[†] It is recognized that in Waldeyer's ring or extranodal sites with 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 longest transverse diameter of a lesion • 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, immunohistochemistry negative
Partial	Partial metabolic response	Partial remission (all of the following):
Lymph nodes and extralymphatic sites	Score 4 or 5[†] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	• ≥ 50% decrease in sum of the product of the perpendicular diameters for multiple lesions of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value • When no longer visible, 0 x 0 mm • For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	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

(Continued on the next page)

Response and Site	PET-CT-Based Response (Patients with FDG-Avid Disease at Screening)	CT-Based Response (Patients Without FDG-Avid Disease at Screening)
No response or stable disease	No metabolic response Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment	Stable disease < 50% decrease from baseline in sum of the product of the perpendicular diameters for multiple lesions of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Target nodes/nodal masses, extranodal lesions		
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease**	Progressive metabolic disease	Progressive disease requires at least 1 of the following cross product of the longest transverse diameter of a lesion and perpendicular diameter progression:
Individual target nodes/nodal masses	Score 4 or 5† with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	An individual node/lesion must be abnormal with: • longest transverse diameter of a lesion > 1.5 cm and • Increase by ≥ 50% from cross product of the longest transverse diameter of a lesion and perpendicular diameter nadir and • An increase in longest transverse diameter of a lesion or shortest axis perpendicular to the longest transverse diameter of a lesion from nadir o 0.5 cm for lesions ≤ 2 cm o 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
Non-measured lesions	None	New or clear progression of pre-existing 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

Abbreviations: CT, computed tomography; FDG, [18F]fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
Modified from Cheson BD, Fisher RJ, Barrington SF, et al. J Clin Oncol 2014;32(27):3059-67.
*A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal, and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), gastrointestinal 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., gastrointestinal 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).

†PET 5-point scale (Deauville Criteria):

- 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

Modification from Lugano Classification for NHL (Cheson et al, 2014):

**Pseudoprogression has been observed in patients receiving a BTK inhibitor. For patients in either arm, a timepoint finding of "disease progression" will require a confirmatory scan at least 4 weeks after the scan that demonstrated possible progression. An exception to the confirmatory scan requirement exists if one or more of the clear, clinical signs of progression detailed in Section 5.6 is present and the investigator believes the progression is unequivocal. Patients may continue study treatment while they wait for the confirmation imaging.

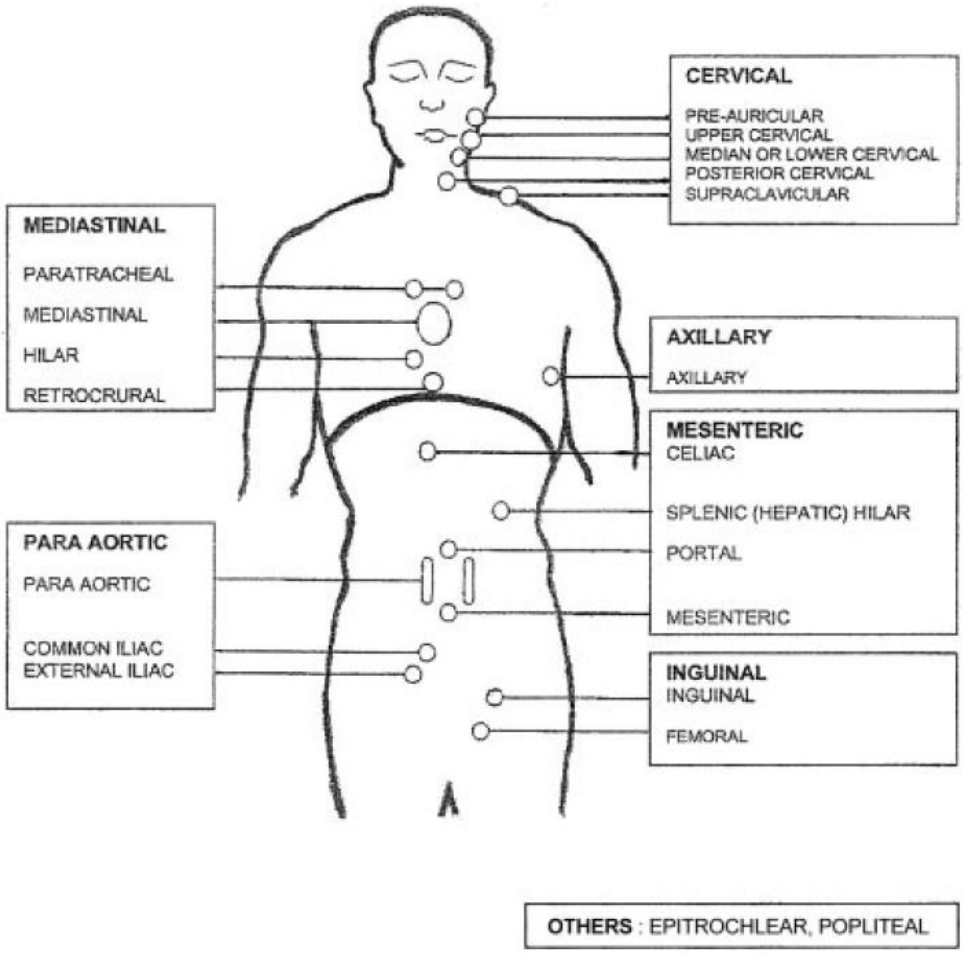
Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

Isolated increase in lymph nodes and/or splenomegaly during periods of zanubrutinib hold will not be considered as progressive disease unless confirmed by a repeat imaging studies at least 6 weeks after restarting study drug administration. The response

category “indeterminate due to zanubrutinib hold” should be selected for such instances. Following the repeat imaging 6 weeks after restarting study drug, response should be in comparison to the imaging at baseline.

APPENDIX 3. DIAGRAM FOR NODAL AREAS IN FLIPI SCORE

This diagram is to be used for counting the number of nodal areas involved. Each rectangle corresponds to a nodal area. Nodal areas considered were cervical, axillary, inguino-crural, para aortic and/or iliac, celiac and/or mesenteric, and other ancillary nodal sites. Involved area (or areas) either clinically or on CT scan (or scans) was quoted as 1 (2 if bilateral) and each patient had between 0 and 8 or more involved areas.



Source: Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004;104:1258-65.

APPENDIX 4. NEW YORK HEART ASSOCIATION CLASSIFICATION

NYHA Class	Symptoms
• I	• Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
• II	• Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
• III	• Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.
• IV	• Severe limitations. Experiences symptoms even while at rest. Mostly bedbound subjects.

APPENDIX 5. ECOG PERFORMANCE STATUS

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 house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

APPENDIX 6. EUROPEAN QUALITY OF LIFE 5-DIMENSIONS 5-LEVELS HEALTH QUESTIONNAIRE

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

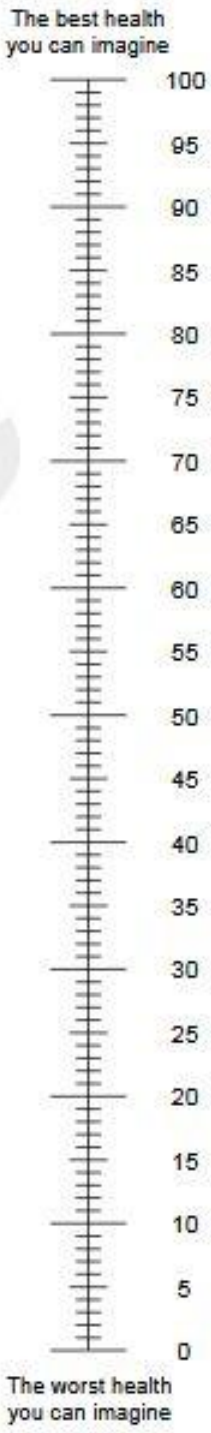
ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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APPENDIX 7. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 8. DOSE MODIFICATION FOR ZANUBRUTINIB WHEN CO-ADMINISTERED WITH STRONG/MODERATE CYP3A INHIBITORS OR INDUCERS

CYP3A	Co-administered Drug	Recommended use
Inhibition	Strong CYP3A inhibitor (eg, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	80 mg once daily
	Moderate CYP3A inhibitor (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit products)	80 mg twice daily
Induction	Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin, St. John's wort)	Avoid concomitant use; Consider alternative agents with less induction potential.
	Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	160 mg twice daily, use with caution; Monitor for potential lack of efficacy.

APPENDIX 9. SCHEDULE OF ASSESSMENTS

Study Period or Visit	**Screening**	**Treatment (1 cycle = 28 days)**							**Post-Treatment Follow-Up**	
Cycle/Week	**–**	**1**			**2 to 6[a]**	**8 then every 2 cycles to 30 (eg, Cycle 8, 10, 12, through Cycle 30)**	**> 30 cycles: every 2 cycles until disease progression**	**Response Evaluation every 12 weeks from Cycle 1 Day 1 for 24 months, then every 24 weeks for 24 months, and then yearly until disease progression[b]**	**Safety Follow-Up[c]**	**Long-Term Follow-Up[d]**
Day	**-35 to -1**	**1**	**8**	**15**	**1**	**1**	**1**	**Any day of the week**	**30 days after end of zanubrutinib** **90 days after end of obinutuzumab**	**Every 12 weeks**
Window (Days)	–		**± 4**		**± 7**	**± 7**	**± 7**	**± 14**	**± 7**	**± 14**
Informed consent, screen number[e]	X									
Medical and cancer history	X									
Eligibility authorization packet[f]	X									
Randomization[g]		X								
Request archival tumor tissue[h]		X								
Obinutuzumab infusion[i]		X	X	X	X	X				
Zanubrutinib dispensing/accountability[j]		X			X	X	X			
Sparse PK (arm A only)[k]		X			Cycle 2					
Safety Assessments[l]										
Vital signs (sitting BP, heart rate, and temperature)	X	X	X	X	X	X	X		X	
Physical examination[m]	X	X	X	X	X	X	X		X	
ECOG performance status	X	X	X	X	X	X	X		X	
12-lead electrocardiogram (local read)[n]	X									
Concomitant medications review	X	X	X	X	X	X	X		X	

Study Period or Visit	Screening	Treatment (1 cycle = 28 days)							Post-Treatment Follow-Up	
Cycle/Week	–	1			2 to 6[a]	8 then every 2 cycles to 30 (eg, Cycle 8, 10, 12, through Cycle 30)	> 30 cycles: every 2 cycles until disease progression	Response Evaluation every 12 weeks from Cycle 1 Day 1 for 24 months, then every 24 weeks for 24 months, and then yearly until disease progression[b]	Safety Follow-Up[c]	Long-Term Follow-Up[d]
Day	-35 to -1	1	8	15	1	1	1	Any day of the week	30 days after end of zanubrutinib 90 days after end of obinutuzumab	Every 12 weeks
Window (Days)	–		± 4		± 7	± 7	± 7	± 14	± 7	± 14
AE review[o]		X	X	X	X	X	X		X	
Efficacy Assessments										
Disease-related constitutional symptoms	X							X		X
Exam of liver, spleen and lymph nodes	X							X		X
Imaging assessments[p]	X							X		X
Bone marrow examination[q]	X							X		X
PRO questionnaires[r]		X						X		X
Survival status and anti-cancer therapy										X
Hematology[s], chemistry[t]	X	X	X	X	X	X	X		X	X
Serum immunoglobulins[u]	X				Cycles 3, 6, 9, 12, then every 24 weeks thereafter until date of centrally confirmed disease progression					
β_2-Microglobulin[v]	X									
Coagulation[w]	X									
Hepatitis B and C testing[x]	X									
Pregnancy test (if applicable; at Screening and every 4 weeks after Cycle 1, Day 1)[y]	X				X	X	X		X	X (every 4 weeks for 90 days)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CR, complete response; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; MRI, magnetic resonance imaging; PET, positron emission tomography; PK, pharmacokinetics; PRO, patient-reported outcome; SAE, serious adverse event.

a. Note that there is no required visit for Cycle 7.
b. Efficacy assessments are performed every 12 weeks after day of first dose for 96 weeks (approximately 24 months), then every 24 weeks for the next 24 months and then yearly until disease progression. To avoid duplication of physical examinations and examination of liver and spleen to fulfill the separate Safety and Efficacy requirements, the following guideline may be used: **It is not necessary to perform duplicate assessments so long as each Cycle Visit and Response Evaluation Visit window is met.**
c. To occur 30 (± 7) days after permanent discontinuation of zanubrutinib and also 90 days after the permanent discontinuation of obinutuzumab (note: the obinituzumab safety follow-up visit may be performed as part of a required visit for patients continuing on zanubrutinib). Patients must continue with the Response Evaluation schedule until date of centrally confirmed disease progression.
d. Response assessments repeat every 12 weeks until centrally-confirmed disease progression, withdrawal of consent, death, or lost to follow-up, whichever occurs first. If a patient has already transitioned to response assessments every 24 weeks or yearly, they may continue to follow the same visit frequency in Long-Term Follow-Up. Patients with centrally confirmed disease progression will be followed up only for survival status and information about their next-line therapy. Survival and next-line therapy follow-up will continue until withdrawal of consent, death, or lost to follow-up, whichever occurs first (contact to collect data will be in person or via phone [with the patient's guardian, if applicable]).
e. This must occur before any study-specific procedures, and may be obtained before the 35-day screening window. Consent must be obtained using the current version of the form approved by the ethics committee.
f. After a patient is screened and the investigator determines the patient is eligible for randomization, study site personnel will complete an Eligibility Authorization Packet and email it to the medical monitor or designee to approve the enrollment in writing. Study site personnel should ensure that a medical monitor-approved Eligibility Packet is in the patient's file before proceeding with study procedures.
g. Eligible patients will be randomized based on number of prior lines of therapy (2 to 3 vs > 3), rituximab-refractory status (yes vs no), and geographic region (China vs ex-China). Central randomization (2:1) will be used to assign patients to 1 of the following 2 arms: zanubrutinib plus obinutuzumab or obinutuzumab monotherapy. Study treatment must commence within 5 days after randomization.
h. If an archival tissue sample is available, it should be sent to the central pathology laboratory for confirmation of tissue diagnosis. It is not required that the archival tissue sample be sent before randomization/treatment assignment
i. Obinutuzumab (arms A and B) will be administered 1,000 mg intravenously on days 1, 8, and 15 of Cycle 1, then 1,000 mg on Day 1 of Cycles 2 to 6, then 1,000 mg every 8 weeks. (At the discretion of the investigator, obinutuzumab may be administered 100 mg on Day 1 and 900 mg on Day 2 of Cycle 1 instead of 1,000 mg on Day 1 of Cycle 1.) Responding patients may continue to receive maintenance obinutuzumab every 8 weeks for an additional 24 months (eg, maximum total duration of obinutuzumab of approximately 30 months [maximum 20 doses]).
j. Zanubrutinib will be administered as two 80-mg capsules by mouth twice a day (160 mg twice a day) with or without food. Patients who progress on obinutuzumab monotherapy are able to crossover to receive obinutuzumab plus zanubrutinib with confirmation of PD and discussion with medical monitor. At the end of Cycle 12, patients in the obinutuzumab arm without a PR or CR have the option to crossover to receive obinutuzumab plus zanubrutinib.
k. Sparse PK samples will be collected from patients randomized to arm A (zanubrutinib plus obinutuzumab) at the following time points: predose (within 30 min prior to zanubrutinib dosing) and 2 hours (± 30 min) post zanubrutinib dose on Day 1 of Cycle 1 and Day 1 of Cycle 2. No sparse PK samples are required during crossover treatment. The times of zanubrutinib administration and PK collection will be recorded.
l. Safety assessments will be conducted on Day 1 of every cycle, unless otherwise specified.
m. Assess systems per standard of care at the study site and as clinically indicated by symptoms. Includes weight (height at screening only).
n. A 12-lead electrocardiogram (ECG) will be performed in triplicate at screening.
o. Collect non-serious AE information from the time of first dose of study drug through safety follow-up. Collect SAE information from the time of signed

informed consent through screen failure or safety follow-up.

p. Tumor assessments, including imaging studies, will be performed at screening, every 12 weeks from Cycle 1 Day 1 for 24 months, then every 24 weeks for 24 months, and then yearly until disease progression. Due to the potential for pseudoprogression cases in this study, patients in both Arms A and B should remain on study treatment while the patient waits for the confirmation scan results. All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. All patients must undergo PET/CT scan during screening. Patients whose disease is not FDG-avid at screening will be followed by CT-based assessments alone. Patients whose disease is FDG-avid at screening will be followed by an integration of PET-CT and CT-based assessments as follows: PET-CT scans are required at screening, end of Cycles 3, 6, and 12, and to confirm a result on CT scan (CR/PR or disease progression); CT scans with contrast are required at all other tumor response assessments. For patients with a contraindication to receiving CT scan IV-contrast (eg, contrast allergy, or other medical contraindication such as renal insufficiency), MRI may be used in place of CT scans. For patients being assessed via MRI, a non-contrast chest CT scan is acceptable, and preferred, in place of a chest MRI to evaluate the lung parenchyma. The same imaging technique (ie, CT, MRI) should be used consistently throughout a patient's time on the study. Copies of all scans will be sent for independent central review for response assessment.

q. Bone marrow biopsy is required under the following conditions during the treatment period: during screening to assess bone marrow involvement of lymphoma; and if clinical and laboratory results demonstrate that a CR has been achieved, in order to confirm a CR. All of the pathology samples will be collected and reviewed by a pathologist from central pathology laboratory.

r. Patients should complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires before the first dose of study drug, and when possible before performing any other procedures. No PRO questionnaires are required during crossover treatment.

s. Complete blood count and differential will be evaluated by a central laboratory. CBC includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count with differential including neutrophils (including bands), lymphocytes, monocytes, eosinophils, and basophils.

t. Serum chemistry will be evaluated by a central laboratory and includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase.

u. Quantitative serum immunoglobulins (IgG, IgM, IgA) will be measured at screening; on Day 1 of Cycle 3, Cycle 6, Cycle 9, and Cycle 12; and then every 24 weeks thereafter until disease progression, withdrawal of consent, death, or lost to follow up, whichever occurs first.

v. β_2-Microglobulin will be assessed by a local laboratory either during screening or predose on Day 1 of Cycle 1 (central lab services may be used in some countries). β_2-Microglobulin may be tested postdose as medically necessary.

w. Prothrombin time, which will also be reported as international normalized ratio, and activated partial thromboplastin time will be evaluated by a central laboratory.

x. Patients who are at risk for HBV reactivation as defined in Section 5.8 will undergo viral load testing at least monthly. Patients who are HCV antibody-positive, but negative for HCV RNA, will undergo viral load testing at least monthly. Hepatitis B and hepatitis C testing will be by local laboratories, but central lab services may be used in some countries – for example if required to achieve the needed sensitivity.

y. For all women of childbearing potential (including those who have had a tubal ligation), a serum pregnancy test will be performed at screening, within 7 days of randomization, and at end of treatment. During treatment, laboratory-based, highly-sensitive pregnancy tests (urine or serum) will be performed within 4 weeks after Cycle 1, Day 1 and then every 4 weeks even if the timing falls outside of the normally scheduled visits. Pregnancy tests must be continued every 4 weeks for at least 90 days after the last dose of study drug (even if the timing falls outside of the normally scheduled visits). Pregnancy tests will be evaluated by local or central laboratories. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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