TITLE: A Phase II study of Obinutuzumab (GA-101) in combination with Ibrutinib (I) for the Treatment of Relapsed Mantle Cell Lymphoma

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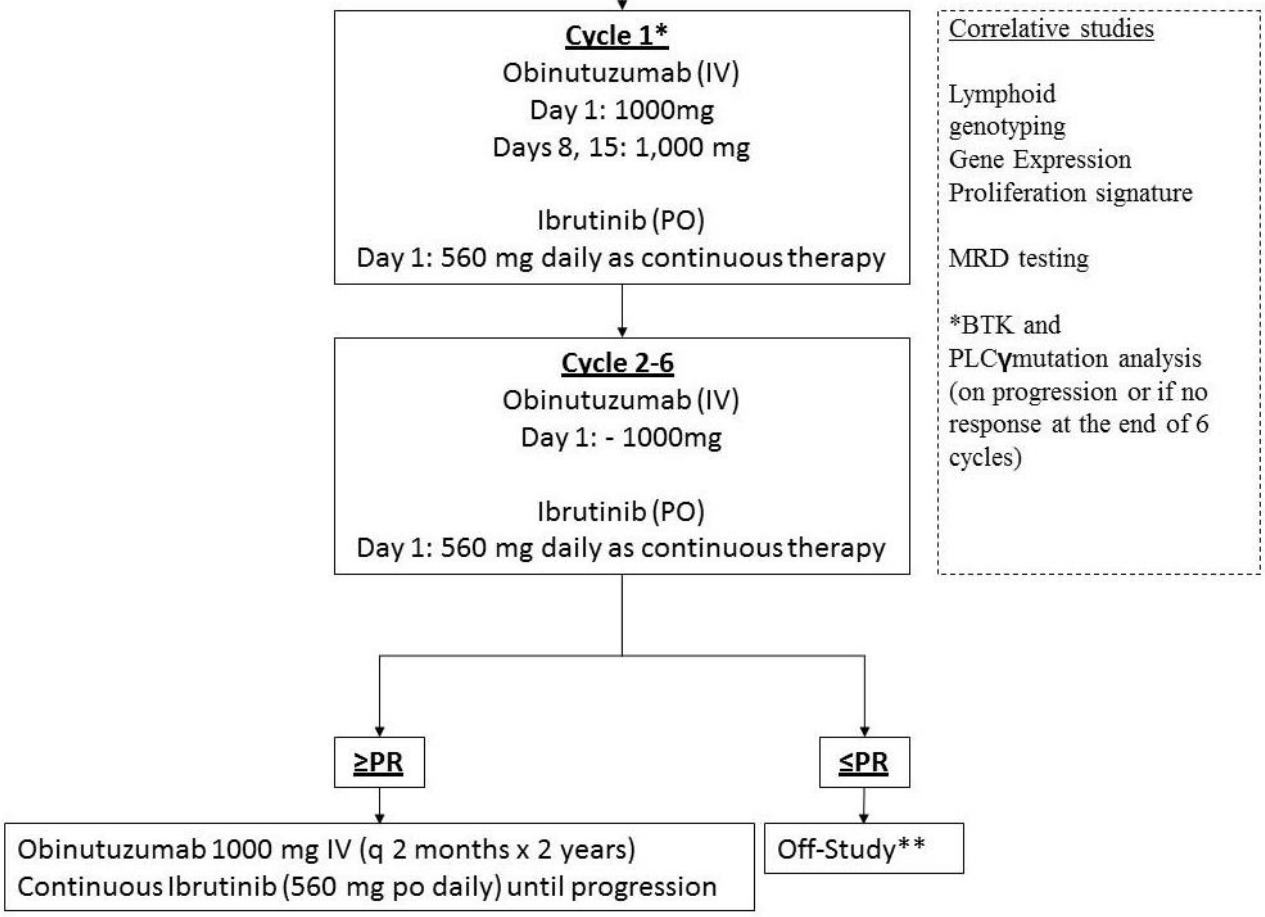
**August 3, 2018 version was uploaded in the IRB system and had to be discarded as the modification was not submitted in a timely manner and the annual review submission was due around the same time. Therefore the modification with the protocol August 8, 2018 was discarded.*

STUDY **SCHEMA**

A Phase II study of Obinutuzumab (GA-101) in combination with Ibrutinib (I) for the Treatment of Relapsed Mantle Cell Lymphoma †



†The study is designed according to Simon's optimal two-stage design.
**patients who have < PR after induction (defined as the first 6 cycles of study treatment) or progress at any time on active therapy will go off the study.

SUMMARY OF CHANGES

As of May 11, 2018, seven patients were enrolled in the Stage I portion of the study with one patient withdrawing a consent prior to the initial response assessment. Of six evaluable patients, five responses (3 CR and 2 PR) were observed. Therefore, the study passed the Stage I futility criteria (stop if 3 or fewer responses out of 6), and it is currently in the Stage II portion of the study. The trial will continue until a total of 20 patients are accrued.

Version 8.1. Summary of Changes	
Section	**Description of Change**
Section 13.3.Informed Consent	Included language for consent/reconsent and modified procedures due to COVID 19

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
anti-HBc	antibody to hepatitis B core antigen
aPTT	activated partial thromboplastin time
BM	bone marrow
ASCO	American Society of Clinical Oncology
AUC	area under the concentration−time curve
BSA	body surface area
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CLL	chronic lymphocytic leukemia
Cmax	maximum concentration observed
CNS	central nervous system
CR	complete response or complete remission
Cru	unconfirmed complete response
CSR	Clinical Study Report
D	Day
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
EC	Ethics Committee
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
F	Phenylalanine
FACS	fluorescent-activated cell sorter
Fc□R	leukocyte receptors for the Fc portion of IgG
FDA	Food and Drug Administration
^{18}F-FDG	^{18}F-fleurodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
GCB	germinal center B cell
GCP	Good Clinical Practice
GCSF	granulocyte-colony stimulating factor
GEP	gene expression profiling

G	GA101
G-FC	GA101 in combination with fludarabine and cyclophosphamide
HAHA	human anti-human antibodies
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	high dose
HTLV	human T-cell leukemia virus
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IHC	Immunohistochemistry
IND	Investigational New Drug
IMC	Internal Monitoring Committee
IRR	infusion-related reaction
IV	Intravenous
IL	Interleukin
IPI	International Prognostic Index
IVRS	interactive voice response system
LD	low dose
LVEF	left ventricular ejection fraction
LVS. D	left ventricular systolic dysfunction
MCL	mantle-cell lymphoma
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NONMEM	Non-Linear Mixed Effect Model
ORR	overall response rate
OS	overall survival
PD	progressive disease
PICC	peripherally inserted central catheter
PK	pharmacokinetic
PET	positron emission tomography
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PR	partial response or partial remission

R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone
SAE	serious adverse event
SD	stable disease
SD	stable disease
SDI	shorter duration of infusion
SLL	small lymphocytic lymphoma
SOC	Scientific Oversight Committee
TLS	tumor lysis syndrome
ULN	upper limit of normal
U.S.	United States
V	valine
WHO	World Health Organization

1. OBJECTIVES

1.1 PRIMARY OBJECTIVE

Best overall response of CR/PR as defined in Section 12.3.1

1.2 SECONDARY OBJECTIVES

a) Toxicity defined as any drug-related AE grade 3 and higher.
b) Progression Free Survival

1.3 EXPLORATORY OBJECTIVES/CORRELATIVES

a) Gene expression profiling using Lymph5Cx test
b) Sequencing using the ion torrent platform (76 gene panel for known mutations in lymphoma)
c) Sequencing of BTK and PLC to evaluate for mutations
d) Minimal Residual Disease Testing (MRD by flow cytometry and targeted sequencing post treatment).

2. BACKGROUND

2.1 MANTLE CELL LYMPHOMA

Mantle cell lymphoma (MCL) accounts for 6% of all Non-Hodgkins Lymphomas (NHL). At the molecular level, MCL is characterized by overexpression of the cell cycle regulator protein cyclin D1 as a result of a chromosomal translocation t(11;14)(q13;q32), which puts the cyclin D1 gene (bcl-1), under the control of the immunoglobulin (Ig) heavy chain enhancer with subsequent overexpression of cyclin D1.[1,2]Although there are exceptions, it is characterized by a unique immunophenotype with co-expression of CD5 and CD20 and lack of CD23 expression.

MCL is a heterogeneous disease with some patients having a more indolent course and others having more aggressive disease. A number of new treatment approaches for previously untreated disease have significantly improved outcomes. However, despite significant improvements in therapy for mantle cell lymphoma (MCL), the overwhelming majority of patients will relapse after initial therapy and ultimately die from their disease. Current treatment options for relapsed disease include chemo-immunotherapy such as the monoclonal anti-CD20 antibody rituximab plus alkylating agents, anthracyclines, and nucleoside analogues. Agents with unique mechanisms of action such as lenalidomide, bortezemib, and mTOR inhibitors (temsirolimus, everolimus) as single agents or in combination with rituximab have also shown efficacy.[3-5] Increasingly, the role of B-cell receptor (BCR) signaling and inhibition has been studied as a potential therapeutic target. Furthermore, use of Ki-67, clinical factors, gene expression, proliferation signatures, and minimal residual disease (MRD) negativity after treatment have emerged as potentially useful tools for risk stratification.[7-9]

To date, the most effective agent for relapsed MCL is Ibrutinib, an oral Bruton's Tyrosine Kinase (BTK) inhibitor, which is now FDA approved for MCL. BTK is activated upon BCR cross-linking and increased constitutive activity has been seen in MCL. Thus, BTK is a rationale therapeutic target.[10-11] Treatment with Ibrutinib has resulted in high response rates, good tolerability, and durable responses in MCL patients. Importantly, however, one-third of patients will fail to respond to ibrutinib and the majority will ultimately progress on treatment. The etiology of primary resistance to single agent ibrutinib remains elusive. One mechanism that has recently been described for acquired resistance in responding patients on treatment is the result of BTK mutations at the ibrutinib site or downstream pathways. Specifically, in CLL and more recently MCL, a serine to cystine (C481S) mutation at the ibrutinib binding site has been appreciated as have mutations in protein lipase C gamma-2 (PLCγ2), a downstream target of BTK.[12,13] However, the rate of ibrutinib failure in MCL cannot be explained by the relatively low frequency of BTK or PLC mutations seen to date. Therefore, developing more effective therapeutic regimens in MCL and understanding potential mechanisms of resistance remains an area of unmet medical need.

The addition of anti-CD20 monoclonal antibody therapy such as rituximab is a mainstay in the treatment of all B cell non-Hodgkin's lymphoma including MCL. Obinutuzumab (GA-101), a type II antibody with enhanced direct

cytotoxicity and ADCC, has shown significant activity across a broad range of NHL. It is currently FDA approved in combination with chlorambucil for the treatment of treatment-naïve CLL where it has shown excellent activity and tolerability[14] and has been shown to be superior to rituximab. The use of obinutuzumab in relapsed NHL, including MCL, was associated with an ORR of 27% including in patients with rituximab refractory disease. In responding cases, there were a number of durable remissions. Importantly, this treatment was well tolerated.[15]

Given the impressive activity and excellent tolerability of both GA-101 and ibrutinib alone and in combination, as well as the need for novel therapies in this population, studying this combination in MCL is warranted. Furthermore, in an era of increasing therapeutic options and more ready access to genomic and pathway analyses, further evaluation of disease biology is an essential component to a better understanding of drivers of therapeutic response as well as treatment resistance. In addition, in MCL, the achievement of minimal residual disease (MRD) after induction has been associated with improved clinical outcomes.[16] However, little is known about rates of MRD after relapse or with novel non "geno-toxic" therapy such as GA-101 and ibrutinib or using more broadly applicable assays such as flow cytometry or next generation sequencing to define MRD. This warrants further investigation.

2.2 STUDY AGENT: OBINUTUZUMAB (GA-101)

Refer to the Investigator Brochure (IB) for additional details.

2.2.1 INVESTIGATIONAL PRODUCT NAME AND DESCRIPTION

Obinutuzumab (also known as RO5072759, GA101) is a humanized glycoengineered type II anti-CD20 monoclonal antibody (mAb). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics: high-affinity binding to the CD20 antigen, high antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP); low complement-dependent cytotoxicity (CDC) activity; and high direct cell death induction.

2.2.2 SUMMARY OF RELEVANT NON-CLINICAL AND CLINICAL PHARMACOLOGY DATA

2.2.2.1 Non-clinical Data

Non-clinical in vitro studies show that obinutuzumab mediates superior induction of direct cell death and effector cell-mediated ADCC and ADCP on a panel of NHL cell lines as compared to the Type I CD20 antibodies rituximab and ofatumumab. Its potency to mediate CDC is significantly reduced as compared to these two antibodies. Obinutuzumab induced complete tumor remission and long term survival (cures) and increased the overall survival in disseminated NHL xenograft models. The efficacious and optimal dose range of obinutuzumab in xenograft models was in the range of 10-30 mg/kg, corresponding to trough levels of 300-600 µg/mL. In addition, obinutuzumab showed efficacy in combination with classical chemotherapeutic agents, such as chlorambucil (Clb), fludarabine and bendamustine. Importantly, the combination of obinutuzumab with chemotherapeutic agents was superior to the combination of these agents with rituximab.

Treatment with obinutuzumab also resulted in potent and superior depletion of B-cells in the peripheral blood and in lymphoid tissues of hCD20 transgenic mice and cynomolgus monkeys. Vaccination studies in cynomolgus monkeys and human CD20 transgenic mice showed that the enhanced efficacy in terms of B-cell depletion of obinutuzumab translated into suppression of de novo antibody responses, but left the protective humoral memory responses intact.

2.2.2.2 Clinical Pharmacokinetic Data

The clinical pharmacology properties of obinutuzumab have been characterized in a number of clinical studies, in patients with CLL or NHL. These studies include Phase I and II monotherapy studies (BO20999 and BO21003), a Phase Ib combination study (BO21000) and a Phase III combination study (BO21004). Population PK modeling was undertaken on all available serum concentration data from studies BO20999, BO21003, BO21000 and BO21004/CLL11 to provide a robust description of the PK behavior of obinutuzumab. This demonstrated that a two

compartment PK model comprising both a linear clearance pathway and a non-linear time varying clearance pathway adequately described serum obinutuzumab concentration data. The initial clearance of obinutuzumab was 2.85 times higher than the steady state clearance which is consistent with a decrease in the time varying clearance component, which is high at the start of treatment and which declines with repeated cycles of obinutuzumab treatment. The time varying clearance pathway is consistent with target mediated drug disposition, such that at the start of treatment when there is a large quantity of CD20 positive cells, this binds obinutuzumab.

With repeated dosing of Obinutuzumab this saturates the pool of CD20 positive cells, hence reducing this component in clearance. The linear clearance pathway is consistent with catabolism of IgG antibodies, and is therefore independent of CD20 positive cells. This analysis further supports the need to minimize the time varying clearance component quickly, and has led to the proposed dose and regimen of 1000 mg in both induction and extended treatment. In the Phase II part of study BO21003, which investigated the 1000 mg obinutuzumab dose taken into Phase III, the PK of Obinutuzumab was assessed in patients with indolent non-Hodgkin's lymphoma (iNHL) who received weekly administrations of 1000 mg of obinutuzumab during the induction phase (4 administrations; Cycle 1 – Cycle 4) followed by an extended maintenance treatment phase of 1000 mg obinutuzumab every 2 months until disease progression. The mean obinutuzumab serum concentration increased markedly over the 4 treatment cycles. Following the final (i.e., fourth) administration of the induction treatment, obinutuzumab serum levels decreased. Overall, mean C_{trough} serum levels of obinutuzumab observed during the maintenance regimen were similar across the 12 maintenance cycles.

In study BO21004/CLL11, a pivotal Phase III study in CLL patients, mean serum obinutuzumab concentrations increased from Cycle 1 to Cycle 2 following administration of obinutuzumab on Day 1/2 (45 patients in Stage 1a received the first 1000 mg dose over 2 days: 100 and 900 mg on Days 1 and 2, respectively), Day 8 and Day 15 of Cycle

From Cycle 3 until Cycle 6, pre- and post-infusion serum concentrations remained constant during the course of treatment. Having the first 1000 mg administered over 2 days did not impair the rapid minimization of the time varying clearance component indicative of depletion of CD20+ tumor cells.

2.3 CLINICAL EFFICACY OF OBINUTUZUMAB IN NON-HODGKIN'S LYMPHOMA

Obinutuzumab is FDA approved for the treatment of previously untreated Chronic Lymphocytic Leukemia in combination with chlorambucil. This approval is based on the promising results seen in the CLL 11 trial which showed high overall response rates and superior PFS as compared to rituximab plus chlorambucil. Obinutuzumab has shown significant activity in additional studies in NHL.[23]

2.3.1 OBINUTUZUMAB MONOTHERAPY

(Studies JO21900, BO20999, and BO21003)

In the monotherapy setting, the proportion of patients who had a CR or PR at the end of treatment ranged from 28% to 58%. Although this was a population with treatment- refractory or relapsed disease, some patients in studies BO20999 and JO21900 achieved a CR by the end-of-treatment assessment.

The Phase I of study BO20999 recruited 21 NHL patients; lymphoma subtypes were follicular (n=13), mantle cell (n=4), diffuse large B-cell (n=1), small lymphocytic (n=1), lymphoplasmacytic lymphoma (n=1) and Waldenström's macroglobulinaemia (n=1). In the Phase I part of the study, 7 patients (33%) had a response at the end of treatment. In the Phase II part, 11 patients (28%) with aNHL and 15 patients (38%) with iNHL had a response at the end of treatment. In Phase II, end-of-treatment response for iNHL was 17% (3 PR) for patients receiving 400/400 mg (n=18) obinutuzumab and 55% (2 CR, 10 PR) in the 1600/800 mg cohort (n=22).

The Phase I part of study BO21003 included 17 patients: 10 with FL, 3 with DLBCL, 2 with lymphocytic lymphoma, and one each with MCL and marginal zone lymphoma. At the end of the (induction) treatment period,

no patients had CR, 5 patients (29%) had PR, 2 patients had progressive disease, and 1 patient had no data.

2.3.2 OBINUTUZUMAB COMBINATION THERAPY

In the Phase Ib chemotherapy combination study, BO21000, 53/56 relapsed/refractory patients (95%) had a response (CR+PR) at the end of treatment; one had PD, one had stable disease (SD) and one had no response assessment due to early withdrawal. In patients with previously untreated B-cell FL, 76/81 patients (94%) responded at the end of treatment; one each had SD and PD, and 3 patients had no response assessment as they withdrew prior to the first response assessment.

The proportion of patients with a CR was higher in this chemotherapy combination study than for the monotherapy studies (relapsed/refractory setting: 39% [11/28 patients] in the obinutuzumab + CHOP arm and 50% [14/28 patients] in the obinutuzumab + FC arm; first-line setting: 39% [16/41 patients] in the obinutuzumab + bendamustine arm and 35% [14/40 patients] in the obinutuzumab + CHOP arm).

2.3.3 OBINUTUZUMAB MAINTENANCE

Obinutuzumab maintenance in responding patients after initial chemo-immunotherapy has been evaluated in NHL. The largest studies to date have been done in follicular lymphoma (FL) and include the GADOLIN and GALLIUM studies. The GALLIUM study us an ongoing randomized Phase III study evaluating 1400 treatment naïve FL patients randomized to Bendamustine plus Rituximab (BR) vs. Bendamustine plus obinutuzumab (B.O.) (www.clinicaltrials.gov; NCT01332968). The GADOLIN trial compared bendamustine vs. B.O. Interim results on the first 396 patients, which were recently reported at the 2015 American Society of Clinical Oncology annual meeting, showed significantly prolonged PFS (29 months vs 14 months) in the B.O. arm. Not surprisingly, the B.O. arm was associated with higher rates of neutropenia (68% vs. 62%) and infusion reactions (33% vs 26%) (Sehn L, et al. J Clin Oncol 33, 2015 (suppl; abstr LBA8502)).

2.3.4 SUMMARY OF OBINUTUZUMAB CLINICAL SAFETY

As of the safety data cutoff date of 2 July 2014, obinutuzumab has been administered to 2863 patients with CLL or NHL, from doses of 50 mg to 2000 mg in monotherapy or in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), fludarabine and cyclophosphamide (FC), bendamustine, or Clb. Overall, the safety of monotherapy Obinutuzumab, or obinutuzumab combination therapy with CHOP, FC, bendamustine, or Clb, was manageable.

The most frequent causes of death were disease progression and adverse events (AEs) describing infectious diseases. This is consistent with the study population and disease being treated. The incidence of fatal events was similar across all ongoing trials. Of particular interest, infusion-related reactions (IRRs) were observed consistently in all obinutuzumab trials; the highest incidence of IRR was at the first infusion with the incidence decreasing rapidly with subsequent infusions. The incidence of IRR observed with combination therapy (FC and CHOP) appears similar to that observed with monotherapy. Furthermore, the incidence of IRR appears to be higher in CLL compared to NHL patients and higher in obinutuzumab- compared to rituximab-exposed patients based on evidence from studies BO21003 and BO21999. There is no clear relationship between obinutuzumab dose and the incidence of IRR based on data from study GAO4768g. In Stage 2 of the pivotal Phase III study, BO21004/ CLL 11, investigating GClb vs RClb in patients with CLL, the incidence of IRR, Grade 3/4 IRR and IRR leading to discontinuation was higher in GClb arm compared to RClb. This study investigated several measures to minimize the risk of IRRs including: use of corticosteroids, withdrawal of antihypertensive treatments, slow infusion, and split dosing and the evidence suggests that these risk minimization measures decreased the risk of IRRs (all grades); however, the impact on the incidence of Grade 3-4 events and treatment discontinuations due to IRR was limited.

Due to the pharmacological class of obinutuzumab, as well as the evidence from monotherapy Phase I trials and chemotherapy combination trials BO21004/CLL11 (Phase III), and GAO4779g (Phase I), the sponsor considers acute thrombocytopenia and thrombocytopenia to be related to obinutuzumab. The main risk associated with

thrombocytopenia is hemorrhage. In trial BO21004/CLL11, the overall incidence of hemorrhagic AEs was comparable between the treatment arms (8% GClb; 7% RClb) with the majority of events being of Grade 1 or 2 severity. However, and importantly, all fatal hemorrhagic events in the GClb arm occurred in Cycle 1 in contrast to such events in the RClb arm which occurred later (beyond 1 year after first administration of study drug). Other AEs of particular interest include Tumor Lysis Syndrome (TLS), neutropenia, infections including progressive multifocal leukoencephalopathy (PML), and hepatitis B virus (HBV) reactivation.

2.3.5 NOTABLE RISKS OF CLINICAL RELEVANCE IDENTIFIED IN CLINICAL INVESTIGATIONS WITH OBINUTUZUMAB

Notable risks of clinical relevance identified in clinical investigations with obinutuzumab were: IRRs, TLS, thrombocytopenia, neutropenia, and infection. Additional risks are presented and discussed in Section 5.5.6 (Adverse Events of Particular Interest) and Section 6 of the IB.

2.3.5.1 Risk of Infusion Reactions

The most frequently observed adverse drug reactions (ADRs) in patients receiving obinutuzumab were IRRs; these occurred predominantly during the first infusion. The incidence and severity of infusion related symptoms decreased substantially with subsequent infusions, with most patients having no IRRs during the second and subsequent administrations of obinutuzumab. The commonly experienced IRRs are characterized by hypotension, fever, chills, flushing, nausea, vomiting, hypertension, and fatigue, amongst other symptoms. In the majority of patients, IRRs were mild or moderate and could be managed by the slowing or temporary halting the first infusion but severe IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g. anaphylaxis). Patients with a high tumor burden (i.e. high peripheral lymphocyte count in CLL [$> 25 \times 10^9$/L]) may be at increased risk of severe IRR.

2.3.5.2 Risk of Tumor Lysis Syndrome

TLS is considered an ADR of obinutuzumab and fatal TLS has been observed among patients exposed to obinutuzumab. Patients who are considered to be at risk of TLS (e.g. patients with a high tumor burden or a high circulating lymphocyte count) should receive adequate tumor lysis prophylaxis with allopurinol (or adequate alternative) and hydration prior to the infusion of obinutuzumab.

2.3.5.3 Risk of Thrombocytopenia and Neutropenia

Neutropenia and thrombocytopenia are also considered as ADRs of obinutuzumab. Febrile neutropenia during treatment has been reported with obinutuzumab. The neutropenia resolved spontaneously or with use of colony-stimulating factors. Patients who experience Grade 3/4 neutropenia should be closely monitored. Primary prophylaxis with granulocyte colony stimulating factors (G-CSF) is recommended as per the ASCO, EORTC, and ESMO guidelines, namely in patients who are ≥ 60 years and/or with comorbidities. Additionally, the use of G-CSF prophylaxis is strongly recommended in Cycle 1 for all patients treated with G-CHOP.

Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. In patients with CLL who were exposed to GClb, fatal hemorrhagic events were also reported in Cycle 1.

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of all concomitant therapies, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

2.3.5.4 Risk of Infection including Progressive Multifocal Leukoencephalopathy

With regard to the risk of infections, due to the pharmacodynamic effect of obinutuzumab, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Obinutuzumab should not be administered in the presence of a severe infection and caution should be exercised when considering the use of obinutuzumab in patients with a history of recurring or chronic infections.

In particular, given that other anti-CD20 antibodies have been associated with HBV reactivation in patients with chronic hepatitis (HBsAg positive) with evidence of prior hepatitis B exposure, or in patients who are carriers (HBsAg negative and hepatitis B core antibody positive). The incidence of reactivation may be exacerbated, particularly when anti-CD20 antibodies are administered with immunosuppressive therapies, such as glucocorticoids or chemotherapy. HBV reactivation (defined as HBV DNA >100IU/mL at least once during the course of a trial) has been observed among patients exposed to obinutuzumab. None of these patients experienced any relevant, serious or non-serious, AEs (e.g. transaminitis, hepatitis, functional liver impairment, jaundice), HBV screening should always be performed before initiation of treatment with obinutuzumab as per institutional guidelines. Patients with active HBV disease should not be treated with obinutuzumab. Patients with positive serology should be referred to a hepatologist or gastroenterologist before start of treatment and should be monitored and managed following local standards to prevent hepatitis reactivation.

Given the profound B-cell depletion following exposure to obinutuzumab and a possible pharmaceutical class effect, the risk of PML may be exacerbated among exposed patients. Patients exposed to obinutuzumab experienced PML. The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (cerebrospinal fluid testing for John Cunningham [JC] viral DNA). Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

2.4 IBRUTINIB

Refer to prescribing information for details.

2.4.1 INVESTIGATIONAL PRODUCT NAME AND DESCRIPTION

Ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d] pyrimidin-1-yl]-1- piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib is a white to off-white crystalline solid. It has a single chiral center and is the R-enantiomer. The investigational drug product, ibrutinib, is an oral formulation containing micronized ibrutinib.

2.4.2 SUMMARY OF RELEVANT NON-CLINICAL AND CLINICAL PHARMACOLOGY DATA

2.4.2.1 Non-clinical Data

In vitro studies have shown that ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity.17 In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited autophosphorylation of BTK, phosphorylation of BTK's physiological substrate, phospholipase-Cγ (PLCγ), and phosphorylation of a further downstream kinase, extracellular signal-regulated kinase.[18]

2.4.2.2 Clinical Pharmacokinetic Data

In vitro preclinical data show that ibrutinib is metabolized primarily by CYP3A. Guidance on concomitant use of

ibrutinib/placebo with CYP3A inhibitors or inducers is provided in Section 5.1.1.

2.4.3 CLINICAL EFFICACY OF IBRUTINIB IN MANTLE CELL LYMPHOMA

2.4.3.1 Ibrutinib Monotherapy in MCL

A Phase I, multicenter, multicohort, open-label, dose-escalation study enrolled 66 subjects with a variety of B-cell malignancies, including chronic lymphocytic leukemia (CLL), Waldenström's macroglobulinemia, follicular cell lymphoma (FL), and MCL. Nine of subject had a diagnosis of MCL and they were all evaluable for response; 7 of the 9 (78%) evaluable subjects achieved an objective response (3 CRs and 4 PRs). The responses have been durable, with a median time on ibrutinib treatment of 8 months (1.3 to 14.7 months) and median PFS of 11.6 months for the 9 subjects.[19]

A Phase II study of single-agent ibrutinib (560 mg daily administered orally) in subjects with relapsed or refractory MCL showed significant activity in MCL patients with or without prior bortezemib exposure. One hundred eleven subjects (63 bortezomib-naïve and 48 bortezomib-exposed) were enrolled in the study. The overall response rate for the 111 treated subjects was 68.0% including a CR rate of 21.0%. The rate of response was similar across all disease risk groups. The estimated median duration of response was 17.5 months and overall survival was not reached at the time of the clinical cutoff. With an estimated median follow-up of 15.3 months, the estimated median PFS was 13.9 months.
Median time to initial response was 1.9 months (range, 1.4 to 13.7 months). The estimated rate of overall survival was 58% at 18 months. Median duration of ibrutinib treatment was 8.3 months (range, 0.7 to 21.4 months).[20]

Ibrutinib is known to effectively cross the blood brain barrier. Recent reports have demonstrated that ibrutinib therapy is highly active and effective in patients with a spectrum of CNS lymphomas including in recurrent/refractory primary CNS lymphoma patients (n=20) where a 75% response rate was seen with excellent tolerability[29]. Activity has also been seen in MCL[30].For example, of 3 patients with active CNS MCL treated with standard dose ibrutinib (560 mg once daily), rapid responses were seen, occurring within 3-8 days. Two CR and 1 PR were observed. CSF sampling demonstrated ibrutinib levels well above the ibrutinib IC50. No additional toxicity was seen[31].

2.4.4 COMBINATION THERAPY

Bendamustine plus rituximab (BR) in combination with ibrutinib was evaluated in 20 patients with relapsed/refractory NHL. In this protocol, patients received bendamustine 90 mg/m2 on Days 1 and 2 with rituximab 375 mg/m2 on Day 1 administered with escalating doses of ibrutinib (280 mg or 560 mg) on Days 1 to 28 every 28 days for a total of 6 cycles. Responding patients could continue ibrutinib alone after Cycle 6 until disease progression or unacceptable toxicity. Nine of the 20 patients had MCL, 7 of whom had relapsed disease. The ORR was 100% (4 CRs and 1 PR) for the 5 evaluable MCL patients. No DLTs were seen. Grade 3/4 adverse events for all patients (n=20) included lymphopenia (15 subjects), neutropenia (5 subjects), rash (3 subjects), and anemia, thrombocytopenia, nausea and vomiting (2 subjects each event).[21]

A phase III international trial comparing BR +/- ibrutinib is currently ongoing and has completed targeted enrollment (clinicaltrials.gov identifier NCT01886872).

2.4.4.1 Ibrutinib plus Rituximab in CLL and MCL

Ibrutinib plus rituximab has been evaluated in CLL in a single are phase 2 study. This combination has not yet been reported for MCL. Patients received 28-day cycles of once-daily ibrutinib 420 mg together with rituximab (375 mg/m(2), intravenously, every week during cycle 1, then once per cycle until cycle 6), followed by continuous daily single-agent ibrutinib 420 mg until disease progression or unacceptable toxicity. This study enrolled 40 patients (36 with relapsed disease). Toxicity was mainly mild to moderate in severity (grade 1-2). Diarrhea occurred in ten (25%) patients (grade 1 in nine patients and grade 2 in one), bleeding events in 14 (33%) patients (eight grade 1 and

five grade 2), nausea or vomiting in 15 patients (38%) (ten grade 1 and five grade 2), and fatigue in seven (18%) patients (four grade 1 and three grade 2). Five patients (13%) had grade 3 infections (two lung infections, one upper respiratory tract infection, one sepsis, and one mucositis), and no grade 4 or 5 infections occurred. One patient had grade 4 neutropenia.[22]

Ibrutinib plus Rituximab has also been evaluated in relapsed/refractory MCL. In a phase II study, 50 patients with R/R MCL were treated with rituximab (375mg/m^2 intravenously weekly×4, then monthly for up to 2 years) and ibrutinib (560 mg orally daily). With a median follow up of 6.5 months (range 1–10), the ORR was 87% with 38% CR rate. All patients with SD or progressive disease had a Ki67 of at least 50%. Of the 33 patients with Ki67 less than 50%, the ORR was 100% with a 48% CR rate. These data suggest that this regimen may be more effective in patients without the blastoid variant, which often is associated with high Ki67. However, the clinical and biologic relevance of this finding should be interpreted with caution given that a Ki67 cut- off of 50% is high by MCL standards and likely the result of trying to stratify outcomes using a relatively small dataset. Grade 3 AEs were neutro- penia (1) and thrombocytopenia (1). Notably six patients developed atrial fibrillation (afib) [Wang *et al*. *Blood (ASH Annual Meeting Abstracts)* abstract 4453].

2.5 STUDY AND DOSE RATIONALE

This single arm Phase II study will combine obinutuzumab and ibrutinib for the treatment of patients with relapsed/refractory MCL. Obinutuzumab will be administered at 1000 mg on days 1, 8, and 15, for cycle 1 and on day 1 of subsequent cycles. Split dosing on days 1 and 2 is performed for CLL. NHL trials dose 1000 mg starting on day 1. That said, similar to other monoclonal antibodies, the dose may be split if deemed appropriate by the treating MD. This is often done for patients with high tumor burden or circulating lymphoma cells.

This dosing schedule results in rapid accumulation of drug, thus maximizing its effects and achieving steady state. The first dose of obinutuzumab may be split over two days if needed per investigator discretion (i.e. 100 mg D1, 900 mg D2). Treatment will be administered for a total of 6 cycles or disease progression, whichever occurs first. This is the current FDA approved dosing strategy for obinutuzumab.

Ibrutinib will be administered at 560 mg orally once daily starting on day 1. For patients who are already receiving ibrutinib (for < 14 days prior to day 1), it can be continued. This is the FDA approved dose for relapsed/refractory MCL. Although there are pre-clinical data suggesting that ibrutinib inhibits ITK in NK/T cells thus inhibiting antigen dependent cellular cytotoxicity (ADCC), a key mechanism for cell killing for rituximab, this has not been seen in pre-clinical models with obinutuzumab or clinically with ibrutinib plus rituximab.[23, 24] Patients with ≥ PR at the end of 6 cycles will then receive obinutuzumab maintenance (1000 mg Q 2 months) for up to two years (a total of 12 doses). This obinutuzumab dose and treatment schedule were selected given the results of PK data obtained from Study BO21003, a Phase I study evaluating post induction obinutuzumab maintenance administered q 3 months in NHL and CLL. Based on the PK results as shown in the figure below (page 82 of the IB), it was determined that the Phase II phase of this study and future studies should include maintenance at 1000 mg every 2 months. No dose reductions will be permitted for obinutuzumab. Dose reductions will be allowed for ibrutinib as described in the package insert (and outlined in section 6.2). Ibrutinib will be discontinued in subjects who are intolerant to ibrutinib despite dose reductions. These subjects will be eligible to stay on study with single agent obinutuzumab if they have completed > 2 cycles of combination therapy and there is no evidence of disease progression.

Figure 2 Mean Serum Obinutuzumab Profiles During 3-Monthly Maintenance Therapy in Patients with NHL (Study BO21003 Phase I)

1-2 patients per dose during the maintenance regimen.

Table 1. Summary of Planned Study Treatment		
Drug	**Dose (route)**	**Duration**
Obinutuzumab	1000 mg (IV)	Cycle 1: Days 1*, 8, 15 if ≥ PR, then continue Obinutuzumab to subsequent cycles Cycle 2-6: Day 1 (q2 cycles, for a total of 2 years)
Ibrutinib		Day 1-28 of each cycle. Administered on an on-going basis until progression [up to 5-years]
*the first dose of obinutuzumab may be split over two days (i.e., 100 mg on day 1 and 900 mg on day 2) if needed per investigator discretion		

Staging studies will include:

- Bone marrow biopsy prior to cycle 1 for all subjects and at the end of cycle 6 for subjects with initial bone marrow involvement.
- PET prior to cycle 1, after cycle 6
- Diagnostic CT prior to Cycle 1, after Cycle 2, and after Cycle 6, then Q 4 months.

2.6 CORRELATIVE STUDIES

A number of clinical and biologic factors have been identified as having prognostic significance in MCL. For example, Mantle Cell International Prognostic Index or 'MIPI' (incorporates age, ECOG performance status, WBC, LDH); MCL cell proliferation (Ki67), and *beta*-2 microglobulin (B2M), have been shown to correlate with clinical outcome with initial treatment. Specifically, patients with high risk MIPI scores have inferior outcomes with median

and overall survival of 29 months after initial chemo-immunotherapy. Similarly, patients with Ki67 > 30% also have poor outcomes.[6,7,9] Although these factors have begun to help risk-stratify MCL patients, they often do not provide additional insight into the biology of the disease. For example, some older patients with splenomegaly and leukemic MCL, who have high MIPI scores, have indolent disease[5]

In an effort to better define disease biology, gene expression profiling has successfully been utilized to diagnose MCL and create a proliferation signature that can predict for inferior outcomes.[8] Although this signature is promising, it has not yet entered standard practice and its relevance in relapsed disease remains unknown. Furthermore, it needs to be prospectively validated especially for relapsed disease and in the era of novel agents. Thus, evaluation of new platforms that can be readily applied to relapsed patients receiving novel agents is warranted.

In addition, minimal residual disease (MRD) negativity at the end of therapy has become an important prognosticator across a number of lymphoid malignancies including chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL).[25, 26] More recently, MRD has been evaluated in MCL using patient specific PCR in patients receiving aggressive chemo-immunotherapy and consolidative autologous stem cell transplant. Patients who achieved MRD negativity after treatment had significantly improved outcomes.[16] However, to date the techniques used to define MRD in MCL are not readily available and may not be broadly applicable outside of a clinical trial. Similar to other prognostic scores, little is known about rates of MRD after relapse or with novel non-"geno-toxic" therapy such as GA-101 and ibrutinib.

Data are also emerging that ibrutinib resistance in some patients with CLL and MCL while on treatment is the result of a mutation in BTK at the ibrutinib binding site or in key downstream targets. For example, of 7 relapsing CLL patients, a serine to cystine (C481S) mutation in BTK at the binding site of ibrutinib was seen in five patients and three distinct mutations in PLCγ2 in two patients. Functional analysis showed that the C481S mutations in PLCγ2 are both potentially gain-of-function mutations that lead to autonomous B-cell-receptor activity.[12] Acquired mutations in the BTK binding site, also resulting in C481S have also been detected in MCL patients after prolonged ibrutinib treatment but not in patients with primary resistance or short duration of drug exposure, suggesting a unique, as of yet, undefined mechanism for patients with primary resistance.[13]

To summarize, clinical factors, Ki67, gene expression profiling/proliferation (GEP) signatures, molecular remission/MRD negativity, and BTK mutations have all shown significant promise in better defining disease biology and prognostic groups; however, it remains clear that additional, more widely available studies are needed that can better define disease biology and further risk stratify patients. Using these approaches may allow for an improved understanding of treatment resistance and outcome especially in the era of targeted agents and ready access to gene expression and genomics data. To this end, we will be conducting a number of correlative studies. Every attempt will be made to biopsy (bone marrow and/or lymph node and/or soft tissue) patients as part of the screening process after enrollment on study and prior to initiation of on-study therapy. In the event tissue is unobtainable, studies will be performed on archival tissue. Patients will also be biopsied at the time of disease progression.

2.6.1 GENE EXPRESSION PROFILING USING NANOSTRING

Formalin fixed, paraffin embedded MCL tissue biopsies or lysates from 10^4 lymphoma cells, qualified by an expert hematopathologist, with matching snap frozen case materials will be collected. 100-200 ng of RNA will be isolated using the Qiagen AllPrep kit. This approach is based on the successful work done by the Lymphoma & Leukemia Molecular Profiling Project (LLMPP) using Nanostring technology (Seattle, WA) for the characterization of cell of origin in diffuse large b-cell lymphoma.[27] NanoString technology (Seattle, WA) will be used to evaluate key MCL genes. To date, the LLMPP has successfully validated probes designed (Lymph5Cx) specifically to evaluate key MCL genes using the nCounter Analysis System (Nanostring, Seattle, WA). In addition to diagnostic verification, with this approach, the LLMPP was able to define key biologic information (proliferation signature) in MCL (Scott et al., Abstract 3016, ASH annual meeting). Dr. Braziel is currently leading this effort at OHSU. Specifically, nucleic acid extraction/RNA preparation will be performed at OHSU using a nano-string prep station.

Samples will then be analyzed using the nCounter system. Proliferation signatures will be defined and correlated with clinical prognostic features including MIPI[5], Ki67, as well as clinical outcomes.

2.6.2 SEQUENCING USING THE ION TORRENT PLATFORM (FOR KNOWN MUTATIONS IN LYMPHOMA)

In conjunction with the OHSU Hematopathology group, the Knight Diagnostic Lab (KDL) has developed a GeneTrails® assay for myeloid and lymphoid hematologic malignancies. The GeneTrails® Lymphoid Genotyping Panel delivers information on 76 predictive and prognostic mutations commonly involved in NHL as well as detecting some mutations that may directly inform targeted or non-targeted treatment options. The panel has a sensitivity of ~5 % mutant allele with strict next generation sequencing quality control parameters. The Genotyping Panel is performed on DNA extracted from blood, bone marrow aspirate or biopsy, lymph nodes, soft tissue, or formalin-fixed, paraffin-embedded (FFPE) tissue. The assay uses next-generation, semiconductor- based massively parallel sequencing (Ion Torrent PGM platform). Input DNA is amplified using the AmpliSeq technology (Ion Torrent), after which the amplicons are modified with adaptors and subjected to emulsion PCR. The final products are sequenced on a 316 or 318 chip. Test parameters are as follows: Input DNA: 20 ng, number of multiplexed amplicons: 701, average read depth per amplicon: 1750. Specimen Requirements include: Peripheral blood: 5 mL EDTA (lavender top tube) or 5 mL Citrate tube or Bone marrow aspirate: 5 mL in EDTA (lavender top tube) or a paraffin block or 10 unstained sections of a bone marrow or lymph node biopsy (4-5 microns).Additional details regarding these specific genes as well as procedures can be found at the KDL website (http://www.knightdxlabs.com). Potential gene targets are frequently evaluated to determine if additional genes need to be added to panel.

2.6.3 SEQUENCING OF BTK TO EVALUATE FOR BTK OR PLC MUTATIONS

To augment the gene trails assay, next generation sequencing may also be utilized to evaluate for mutations in specific genes that may not be included in the gene trails panel, such as BTK and PLCγ2. Patients not responding to initial therapy at 6 months or who progress on therapy, will have BTK and PLCγ evaluated. The same sample acquisition/isolation techniques as described above will be utilized for this approach.

2.6.4 MRD BY FLOW CYTOMETRY AND SEQUENCING POST TREATMENT

Evaluation of MRD by flow cytometry at the end of treatment is routinely performed at OHSU for patients with hematologic malignancies including ALL, CLL, and MCL. For patients with bone marrow involvement prior to the initiation of therapy who achieve a radiographic CR after the completion of treatment, bone marrow samples will be obtained 2 months after completion of therapy and prior to initiation of maintenance obinutuzumab. For those subjects not in CR after induction and who had marrow involvement prior to initiation of therapy, MRD testing should be evaluated if/once nodal CR achieved. This assay uses 8 color flow cytometry for lymphoid specific antigens with a sensitivity of 1:10,000 and will be performed as part of routine clinical care. For select cases that are MRD negative by flow cytometry, Next Generation Sequencing using the aforementioned ion torrent platform for MCL specific genes found on pre-treatment specimens will be performed and correlated with flow cytometry results.

3. STUDY POPULATION

3.1 INCLUSION CRITERIA

3.1.1 Subjects must have a diagnosis of Relapsed or Refractory Mantle Cell Lymphoma as follows:

a) Diagnosis of MCL must include morphology and expression of either cyclin D1 in association with other relevant markers (eg, CD19, CD20, CD5) or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR).

b) Relapsed or refractory disease, which is defined as no response or progressive disease to prior treatment if the prior treatment comprised any of the following:

i. 1 regimen containing an anti-CD20 antibody administered for ≥ 2 doses, and/or
ii. ≥ 1 regimen containing 1 cytotoxic agent (e.g., bendamustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin) administered for 2 cycles.

3.1.2 At least 1 measurable site of disease according to Revised Response Criteria for:

- Malignant Lymphoma (Cheson Criteria). The site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions.

3.1.3 Age ≥ 18 years. Both men and women and members of all races and ethnic groups will be included.

3.1.4 ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see Appendix A).

3.1.5 Subjects must have normal organ and marrow function as defined below:

- absolute neutrophil count (ANC) ≥ 1.0 K/cu mm*
- Platelets (plt) ≥ 50 K/cu mm*
- total bilirubin ≤ 2.5 X institutional limits
- AST(SGOT)/ALT(SGPT) ≤ 2.5 X institutional upper limit of normal
- Creatinine ≤ 2

**for subjects with plt < 50 K/cu mm or ANC < 1.0 K/cu mm due to significant marrow involvement by MCL, ANC must be > .5 K/cu mm and plt > 25 K/cu mm*

3.1.6 Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 18 months after last dose of obinutuzumab, or 1 month after the last dose of ibrutinib, whichever is later. For males, these restrictions apply for 180 days after the last dose of obinutuzumab or 3 months after the last dose of ibrutinib, whichever is later.

3.1.7 Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.2 EXCLUSION CRITERIA

3.2.1 Major surgery within 4 weeks of drug administration

3.2.2 Diagnosed or treated for malignancy other than MCL, except:

a) Malignancy treated with curative intent and with no known active disease present for ≥ 2 years before randomization (the exception is prostate cancer)

b) Adequately treated non-melanoma skin cancer or melanoma in situ without evidence of disease.

c) Adequately treated cervical carcinoma in situ without evidence of disease.

d) Asymptomatic prostate cancer managed with “active surveillance.”

e) Localized prostate cancer treated with definitive treatment including radiation or surgery. Patients on adjuvant hormone deprivation treatment such as Lupron are eligible. Patients with known metastatic disease are ineligible.

3.2.3 History of stroke or intracranial hemorrhage within 6 months prior to randomization.

3.2.4 Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).

3.2.5 Vaccinated with live, attenuated vaccines within 4 weeks of randomization.

3.2.6 Requires treatment with strong CYP3A inhibitors (see section 5.5.1).

3.2.7 Subjects who have had standard cytotoxic chemotherapy within 3 weeks prior to entering the study or those whose adverse events due to agents administered more than 3 weeks earlier have not recovered to ≤ Grade 1. This excludes alopecia and hematologic adverse events.

3.2.8 Subjects who have had radiotherapy within 2 weeks prior to entering the study or those whose adverse events due to radiotherapy more than 2 weeks earlier have not recovered to ≤ Grade 1.

3.2.9 Subjects who have received investigational or approved oral or "targeted" agents (such as SYK, PI3K, bcl-2, BTK inhibitors) or lenalidomide within 1 week prior to entering the study or those whose adverse events due to agents administered more than 1 week earlier have not recovered to ≤ Grade 1. This excludes hematologic adverse events. The exception is subjects who are currently receiving ibrutinib (for < 14 days). In this case, ibrutinib can be continued.

3.2.10 Subjects who have received monoclonal antibodies (such as Rituxan) within 1 week prior to entering the study or those whose adverse events due to agents administered more than 1 week earlier have not recovered to ≤ Grade 1. This excludes hematologic adverse events.

3.2.11 Subjects who are actively receiving any other investigational agents.

3.2.12 History of severe allergic reactions attributed to compounds of similar chemical or biologic composition as obinutuzumab or ibrutinib or other agents used in the study

3.2.13 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.14 Pregnant or lactating women are excluded from this study.

3.2.15 Known history of human immunodeficiency virus (HIV) or active Hepatitis C.

3.2.16 Virus or active Hepatitis B Virus infection. Patients who are HBcAb positive may be eligible as long as there is no evidence of active infection with negative Hep B by PCR. In this case, Hep B PCR must be monitored monthly.

3.2.17 Any uncontrolled active systemic infection requiring intravenous (IV) antibiotics.

3.2.18 Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.

3.2.19 Patients previously treated with ibrutinib > 14 days are ineligible. No drug intervention or cessation is required for patients already receiving ibrutinib prior to initiation of on-study therapy.

3.2.20 Active graft vs. host disease (GVHD).

3.2.21 Ongoing glucocorticoids (prednisone > 10 mg daily, or equivalent). Higher doses (> 10 mg daily) are permitted for up to 5 days to help control disease related symptoms

3.3 PROHIBITIONS AND RESTRICTIONS

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib: For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib and/or obinutuzumab should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguinous drainage or the need for drainage tubes.

For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib and obinutuzumab should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib and/or obinutuzumab, it is not necessary to hold ibrutinib and/or obinutuzumab for these procedures.

For emergency procedures, ibrutinib and/or obinutuzumab should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

4. REGISTRATION PROCEDURES

4.1 SUBJECT REGISTRATION

Detailed Instructions for subject registration can be found in the separate study operations manual.

This is a phase II trial with an intention to treat all patients who are enrolled in this clinical trial. There is no randomization for treatment. Potential subjects will be seen by study investigators study as new patient, consult, or follow-up visits. Referral of potential subjects to co-investigators of this study is made as part of standard of care, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of relapsed or refractory MCL.

Registrations from all consented subjects must be entered into the Knight Clinical Research Management System (CRMS). Registration of OHSU patients will include the minimum of the following:

- A completed Subject Enrollment Form
- A completed Eligibility Checklist signed by the investigator
- Signed copies of the most recently IRB-approved, informed consent form and HIPPA authorization

4.2 MULTICENTER REGISTRATION

The OHSU coordinating center study team will manage subject registration. Investigators at participating sites will identify eligible subjects and send screening materials with source documents that support eligibility to OHSU in real time and in accordance with study protocol. Designated Knight clinical staff must review and verify eligibility before the participating site may enroll and treat its subject. The OHSU coordinating center team will verify completeness of documents, enter registration information into eCRIS, and assign a study number/identifier. The coordinating center will send an email to the participating site indicating whether or not the subject is eligible, verify registration, and assign a participant number/identifier.

Registration will include a minimum of the following:

- A completed Subject Enrollment Form
- A completed Eligibility Checklist signed by the investigator
- Signed copies of the most recently IRB-approved, informed consent form and HIPAA authorization

Each participating research site is expected to maintain a screening log of all participants who are approached for the study. The log documents an explanation for exclusion due to screen failure. This log should be submitted to the OHSU coordinating center on a regular basis. Participating sites are required to retain, in a confidential manner, sufficient information on each participant so that the participant may be contacted should the need arise.

5. TREATMENT PLAN

5.1 AGENT ADMINISTRATION

The treatment described herein is an outpatient regimen. Therefore, treatment will primarily be administered on an outpatient basis.

Obinutuzumab: Treatment induction will consist of obinutuzumab 1000 mg (IV) administered on days 1, 8, 15 for cycle 1 and on day 1 for subsequent cycles (cycles 2-6). Each cycle is 28 days. The first dose of obinutuzumab may be split over two days if needed per investigator discretion (i.e. 100 mg D1, 900 mg D2). Responding patients (i.e., ≥ PR) after initial induction will proceed with obinutuzumab maintenance 1000 mg Q2 cycles.

Ibrutinib: Will be self-administered (4 x 140 mg tabs, total dose 560mg daily) starting on day 1 of treatment.

Infrequently patients with high tumor burden receiving monoclonal antibodies such as rituximab or obinutuzumab may be admitted for initial tumor lysis monitoring as per standard of care. Thus, inpatient admission for initial obinutuzumab administration may be done per the discretion of the treating physician. Reported adverse events and potential risks associated with *obinutuzumab and ibrutinib* are described in Section 7.

Planned admission for obinutuzumab administration will not be considered an adverse event (AE).

Appropriate dose modifications for *ibrutinib* are described in Section 6.2. No dose reductions will be allowed for obinutuzumab. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

5.2 OBINUTUZUMAB ADMINISTRATION AND SUPPORTIVE CARE

Obinutuzumab has been associated with infusion reactions. To help prevent infusion reactions, pre-medications with dexamethasone, Tylenol, and an anti-histamine (Benadryl or loratadine) will be administered per standard of care and institutional guidelines. Additional supportive measures will include interruption of obinutuzumab infusion, IV hydration, meperidine (for rigors), anti- emetics, and corticosteroids (dexamethasone, hydrocortisone, or methylprednisolone). Epinephrine will also be available in the event of anaphylaxis. All order sets will include these supportive measures as per current standard of care.

5.2.1 INFUSION RATE

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision by the investigator at all times. Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. Obinutuzumab will be provided by the Sponsor to up to four investigational centers.

5.2.1.1 Infusion rate (per SOC guidelines):

Cycle 1 (day 1 [C1D1]): Initiate infusion at 50 mg/hour for 30 minutes; if tolerated, may escalate rate in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.

All subsequent infusions: If no reaction or grade 1 reaction to previous infusion and the final infusion rate was 100 mg/hour or faster, initiate infusion at 100 mg/hour for 30 minutes; if tolerated, may escalate rate in increments of 100 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. If a grade 2 or higher infusion reaction occurred during the previous infusion, initiate infusion at 50 mg/hour for 30 minutes; if tolerated, may escalate rate in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. Rate may be adjusted if clinically indicated, at the discretion of the RN or investigator. Refer to FDA approved prescribing information and www.gazyva.com.

Vital Signs (all infusions): Vital signs should be taken every 15 minutes for the first hour of infusion until stable, then every 30 minutes with rate escalation, until completion of infusion. Pulse oximetry on room air should be performed at baseline and as needed if dyspnea occurs. Epinephrine 1 mg/ml, diphenhydramine 50 mg IV and hydrocortisone 100 mg IV should be readily available during obinutuzumab infusion

5.2.1.2 Premedication Guidelines to prevent infusion reactions:

C1D1*:* All patients should receive acetaminophen (650 to 1,000 mg) and an antihistamine (e.g., diphenhydramine 25-50 mg) at least 30 minutes prior to infusion. In addition, an IV glucocorticoid (dexamethasone 20 mg or methylprednisolone 80 mg) should be administered at least 1 hour prior to infusion.

All subsequent infusions: All patients should receive acetaminophen 650 to 1,000 mg at least 30 minutes prior to infusion.
If patients experienced grade 1 or 2 infusion-related reaction with previous infusion: Administer an antihistamine (e.g., diphenhydramine 25-50 mg or loratadine 10 mg) in addition to acetaminophen at least 30 minutes prior to infusion.

If patients experienced a grade 3 infusion-related reaction with previous infusion **or** have a lymphocyte count >25,000 cells/mm^3 prior to next treatment: Administer an IV glucocorticoid (dexamethasone 20 mg or methylprednisolone 80 mg) at least 1 hour prior to infusion, in addition to acetaminophen and an antihistamine at least 30 minutes prior to infusion.

5.2.2 INFECTIONS

Like other monoclonal anti-CD20 antibodies (rituximab, ofatumumab), treatment with obinutuzumab can potentially lead to infectious complications. Viral reactivation including hepatitis, which can potentially lead to fulminant hepatic failure, can occur. Therefore, patients with active Hepatitis B infection are excluded from study participation.

Also, given the potential for HSV/VZV reactivation, all subjects will receive antiviral prophylaxis such as:

- acyclovir 800 mg po once daily or 400 mg po twice daily BID, **OR**
- valacyclovir 500 mg daily

HSV/VZV prophylaxis will continue throughout the induction phase of obinutuzumab plus ibrutinib (for the first 6 cycles). Subjects who are allergic/intolerant to or refuse these agents may discontinue antiviral prophylaxis and stay on study if a) he/she does not have a known history of HSV/VZV and b) after discussion with the PI and coordinating center. Additional prophylactic antifungals or anti-bacterials are not required but may be administered per the discretion of the treating physician per institutional standards.

5.2.3 TUMOR LYSIS SYNDROME

Patients with high tumor burden and/or high circulating lymphocyte count (> 25 x 10^9/L) are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with antihyperuricemics (e.g., allopurinol) and hydration beginning 12–24 hours prior to the infusion of obinutuzumab. For treatment of TLS, correct electrolyte abnormalities, monitor renal function, and fluid balance, and administer supportive care, including dialysis or rasburicase as indicated.

5.2.4 WORSENING OF PRE-EXISTING CARDIAC CONDITIONS

Infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of a physician. Hypotension may occur during intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication. Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period.

5.3 IBRUTINIB ADMINISTRATION AND SUPPORTIVE CARE

With formulary change, subjects are instructed to take 1 tablet for a dose of 560 mg (which used to be 4 capsules of Ibrutinib for a dose of 560 mg) by mouth once daily, starting on **Day 1** of Cycle 1. Ibrutinib is to be taken around the same time each day with approximately 240 mL of water (i.e., 8 ounces). Ibrutinib should be swallowed whole and should not be opened, broken, or chewed. Ibrutinib should be taken at least 30 minutes before eating or at least 2 hours after a meal.

If Ibrutinib is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

5.4 CONSIDERATIONS FOR IBRUTINIB PLUS OBINUTUZUMAB

5.4.1 TUMOR LYSIS SYNDROME

Obinutuzumab has been associated with tumor lysis syndrome (TLS). Therefore, it is recommended that patients with high tumor burdens receive allopurinol therapy starting 48 hours prior to the initiation of treatment and have frequent TLS lab monitoring per the treating investigator's discretion.

5.4.2 BONE MARROW SUPPRESSION

Obinutuzumab and ibrutinib treatment can lead to anemia and thrombocytopenia requiring transfusions as well as significant neutropenia. Granulocyte Colony stimulating factors (filgrastim, pegfilgrastim) are not required but may be administered per the discretion of the treating physician. Ibrutinib dose reductions as described in section 6.2.

5.4.3 NEUTROPENIC FEVER

Will be treated per institutional standards.

5.5 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES USE OF IBRUTINIB WITH CYP3A INHIBITORS OR INDUCERS

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors. Strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, consider reducing the ibrutinib dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

Subjects must discontinue all herbal and nutritional supplements. If the investigator determines the supplement to be benefitting the patient, the subject may stay on the supplement ONLY AFTER it has been reviewed by an oncology certified pharmacist and deemed NOT to have significant interactions with ibrutinib. If the interaction or risk is unknown, subjects will be required to discontinue all herbals and/or supplements.

Examples of inhibitors, inducers, and substrates are included below:

5.5.1 INHIBITORS OF CYP3A

Examples of inhibitors and inducers of CYP3A can be found at the following website:
http://medicine.iupui.edu/clinpharm/ddis/table.aspx

AND
http://www.pharmacologyweekly.com/content/pages/ online-drug-therapy- tables.[17, 34] The list below reflects information obtained from the Indiana University, Division of Clinical Pharmacology, Indianapolis, IN website on July 2013.

Strong inhibitors: Indinavir, Nelfinavir, Ritonavir, Clarithromycin, Itraconazole, Ketoconazole, Nefazodone, Saquinavir, Telithromycin

Moderate inhibitors: Aprepitant, erythromycin, diltiazem, fluconazole, grapefruit juice, Seville orange juice, verapamil

Weak inhibitors: cimetidine

All other inhibitors: amiodarone chloramphenicol, boceprevir, ciprofloxacin, delaviridine, diethyl-dithiocarbamate, fluoxetine-metabolite, norfluoxetine, fluvoxamine, gestodene, imatinib, mibefradil

5.5.2 INDUCERS OF CYP3A

Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone.

Because there is a potential for interaction of *study agent(s)* with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The principal investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.6 DURATION OF TREATMENT

In the absence of treatment delays due to adverse events, treatment may continue up to 2 years or until one of the following criteria applies**:**

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s) including:
    - Grade 4 infusion reactions
    - Grade 4 bleeding
- Subject decides to withdraw from the study,
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator, or
- For any reason, at the Sponsor’s (OHSU) discretion.

Additionally;

- Need to hold Obinutuzumab for > 14 days due to the toxicities listed in section 6.1,
- Need to hold ibrutinib for > 14 days or for those who require more than 3 dose reductions due to the toxicities listed in Section 6.2 if occurring prior to Day 56 of therapy.

Subjects who need to discontinue ibrutinib due to the toxicities in Section 6.2 after day 56 (after completion of 2 cycles of combination therapy) are eligible to stay on study for ongoing treatment with Obinutuzumab as outlined in Section 6.2.

5.7 DURATION OF FOLLOW-UP

Subjects will be followed up to 3 years or until disease progression. Subjects removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

If a subject withdraws consent for further treatment, it is important to clarify and document the subject's willingness to continue in the follow-up phase of the study.

5.8 CRITERIA FOR REMOVAL FROM STUDY

Subjects will be removed from study when any of the criteria listed in Section 5.6 apply. The reason for study removal and the date the subject was removed must be documented in the Case Report Form.

5.9 STUDY DISCONTINUATION

There are pre-planned stopping rules for this study for toxicity for the entire cohort based on the incidence of > Grade 2 treatment related toxicity. The study may be discontinued if:

- *The incidence or severity of adverse events indicates a potential health hazard to subjects.*
- *Subject enrollment is not proceeding at a pace that is compatible with trial completion within a reasonable amount of time so that the data are informative and the field moves forward.*

5.10 DEFINITION OF DOSE-LIMITING TOXICITY

The following events are dose-limiting toxicities. Note that these events are only considered DLTs if assessed as related to the study drug:

- Grade 3 neutropenia or thrombocytopenia lasting > 14 days
- Grade 3 thrombocytopenia with significant bleeding
- Grade 3 diarrhea lasting > 7 days despite holding treatment or therapeutic intervention
- Grade 4 neutropenia or thrombocytopenia lasting > 7 days
- Grade 4 infusion reaction
- Grade 4 bleeding
- Grade 4 diarrhea > 48 hours despite holding treatment or therapeutic intervention
- Grade 4 infection
- Death

Management and dose modifications associated with the above treatment related adverse events are outlined in Section 6.

6. DOSING DELAYS/DOSE MODIFICATIONS

All subjects will be evaluated for potential drug related toxicities at each visit. Dose interruptions or reductions will be permitted. In some cases, non-hematologic toxicities may be attributable to one drug but not the other. In this case a subject may have one drug withheld while the other is continued.

If a Grade 3 hematologic DLT occurs, repeat CBC 2x/month (Day 1 and Day 15) will be performed. If a Grade 4 hematologic DLT occurs, repeat CBC weekly until toxicity resolves to < Grade 2.

6.1 OBINUTUZUMAB

No dose reductions for obinutuzumab will be permitted. Dose interruptions/delays will be allowed. For infusion reactions, appropriate changes in infusion rate and pre- medications/supportive care will be utilized as described in Section 5.2. Subjects experiencing a Grade 4 infusion reaction will be removed from the study. Obinutuzumab may be delayed for up to 14 days for toxicity irrespective of causality. If the toxicity is present on D8 of Cycle 1, Obinutuzumab should be omitted. Obinutuzumab may also be delayed per the discretion of the treating physician.

Dose interruptions/delays must be performed for the following toxicities, when related to obinutuzumab:

- Grade 3 or greater neutropenia with infection or fever.
- Grade 4 neutropenia (ANC < 0.5 x 10^9/L [< 500/mm^3]) >14 days
- Grade 3 thrombocytopenia (platelets < 50 x 10^9/L [< 50,000/mm^3]) in the presence of significant bleeding.
- Grade 4 thrombocytopenia (platelets < 25 x 10^9 /L [< 25,000/mm^3])
- Grade 3 or greater non-hematological toxicity

6.2 IBRUTINIB

Dose reductions will be allowed for ibrutinib drug-related toxicities as defined in **Table 2**. Ibrutinib will be discontinued in subjects who are intolerant to ibrutinib despite dose reductions. Treatment with ibrutinib may be held for up to 14 days. If treatment is held for > 14 days, ibrutinib must be discontinued for the remainder of the study. These subjects will be eligible to stay on study with single agent obinutuzumab if they have completed > 2 (up to day 56, which can include dose interruptions and/or reductions) cycles of combination therapy and there is no evidence of disease progression. Specifically, dose reductions will be performed for the following ibrutinib drug related toxicities:

- Grade 3 or greater neutropenia with infection or fever
- Grade 4 neutropenia (ANC < 0.5 x 10^9/L [< 500/mm^3]) > 14 days.
- Grade 3 thrombocytopenia (platelets < 50 x 10^9/L [< 50,000/mm^3]) in the presence of significant bleeding.
- Grade 4 thrombocytopenia (platelets < 25 x 10^9 /L [< 25,000/mm^3]).
- Grade 3 or greater non-hematological toxicity

Table 2. Recommended Management for Ibrutinib-related toxicities	
Occurrence	***Action***
First	*Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level*
Second	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (3 capsules [i.e., 420 mg daily])
Third	*Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (2 capsules [i.e., 280 mg daily])*
Fourth	*Discontinue study drug*

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. To inform the potential trial stopping rules (DLTs as defined in section 5.10) and the secondary endpoint of grade 3 or higher toxicities, we will report Gr. 3 or higher toxicities irrespective of attribution and denote if these satisfy criteria for a DLT. Any other (i.e. < Gr. 3) AE (unless otherwise specified i.e. tumor lysis), will not be reported. In addition, we will follow the list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) to determine whether the event requires expedited reporting.

7.1 ADVERSE EVENTS AND POTENTIAL RISKS LISTS

7.1.1 OBINUTUZUMAB

In monotherapy studies (BO20999 and BO21003) which included 243 patients (205 NHL, 38 CLL) thirty (79%) CLL and 84 (41%) NHL patients experienced Grade 3 or 4 AEs. Among CLL patients, the most frequent Grade 3 or 4 AEs were infusion reactions (IRRs) (n=11; 29%) and neutropenia (n=13; 34%). Among NHL patients, the most frequent Grade 3 or 4 AEs were IRRs (n=18; 9%) followed by neutropenia (n=14; 7%) and lymphopenia (n=12; 6%). Four (11%) CLL and 11(5%) NHL patients experienced AEs leading to withdrawal of obinutuzumab. The most frequent AE leading to obinutuzumab withdrawal among NHL patients was IRRs (n=3; 1%). Other events occurred in one patient each. Among the 4 CLL patients who experienced AEs leading to obinutuzumab

withdrawal, 3 discontinued due to IRR and 1discontinued due to interstitial lung disease. The table below (also Table 15 from page 98 of IB) represents the incidence of fatal AEs, Grade 3 or 4 AEs, treatment withdrawals due to AEs, and AEs of particular interest in monotherapy NHL/CLL studies. Another Japanese monotherapy study (JO21900) of 12 NHL patients had a similar toxicity profile (Table 20, IB page 93).

Figure 2. Summary of deaths an AEs in patients with iNHL by treatment arm (obinutuzumab or rituximab) Study BO1003 Phase II

	Rituximab (N=86) Patients, n (%)		Obinutuzumab (N=87) Patients, n (%)	
Death	11[a]	(12.8)	18	(20.6)
Adverse Event leading to death	3	(3.5)	4	(5)
SAE	17	(19.8)	21	(24.1)
SAE leading to withdrawal from treatment	5	(5.8)	6	(6.9)
SAE leading to dose interruption	1	(1.1)	0	(0)
Related SAE	7	(8.1)	8	(9.2)
Severe AE	29	(33.7)	33	(37.9)
AE leading to withdrawal from treatment	10	(11.6)	10	(11.5)
AEs of particular interest[b]				
Infusion-related reaction	44	(51.2)	70	(80.4)
Serious	1	(1.2)	2	(2.3)
Leading to antibody withdrawal[c]	1	(2.3)	3	(4.3)
Infection	42	(48.8)	41	(47.1)
Serious	4	(4.7)	7	(8.0)
Leading to antibody withdrawal[c]	3	(7.1)	1	(2.4)
Neutropenia	9	(10.5)	6	(6.8)
Serious	4	(4.7)	3	(3.4)
Leading to antibody withdrawal[c]	1	(11.1)	0	(0)
Thrombocytopenia	0	(0)	2	(2)
Serious	0	(0)	0	(0)
Leading to antibody withdrawal[b]	0	(0)	0	(0)
Tumor Lysis Syndrome	0	(0)	0	(0)
Serious	0	(0)	0	(0)
Leading to antibody withdrawal[c]	0	(0)	0	(0)

Percentages based on N

[a] one patient in the rituximab arm died due to graft versus host disease post-transplant and is not included in this table

[b] Defined based on grouped preferred terms

[c] Percentages based on the number of patients with at least one AE

In combination studies, obinutuzumab has been combined with CHOP, FC, and bendamustine. Deaths due to causes other than disease progression occurred in 5 patients in the obinutuzumab + FC arm and in 1 patient in the obinutuzumab + CHOP arm. Among the 5 deaths, one case (fatal PML) was considered as related to obinutuzumab. The other causes of death were all considered to be unrelated to obinutuzumab: Parkinson's disease, chronic obstructive pulmonary disease, ascites (the patient died from the event of ascites more than 6 months after interruption of obinutuzumab), and cardiac arrest. The table below (IB page 106) is a summary of significant AEs in patients treated with combination chemo-immunotherapy.

Table 37 Summary of Deaths and Adverse Events in Previously Untreated CLL Patients (Study GAO4779g)

	G-FC (N=21) Patients, n (%)	G-Benda (N=20) Patients, n (%)
Death	1 (4.8)	1 (5)
AE leading to death	0 0	1 (5.0%)
SAE	6 (28.6)	11 (55.0)
Grade 3 or 4 AE	18 (85.7)	17 (85.0)
Related Grade 3 or 4 AE	17 (81)	14 (70)
Any treatment withdrawal due to AE	7 (33.3)	2 (10.0)
AEs of particular interest[a]		
Infusion-related reaction	20 (95.2)	18 (90.0)
Serious	1 (4.8)	4 (20.0)
Leading to withdrawal of any treatment[b]	1 (5.0)	0 (0)
Infection	11 (52.4)	9 (45.0)
Serious	3 (14.3)	1 (5.0)
Leading to withdrawal of any treatment[b]	1 (9.1)	0 (0)
Neutropenia	8 (38.1)	11 (55.0)
Serious	4 (19.0)	3 (15.0)
Leading to withdrawal of any treatment[b]	3 (37.5)	2 (18.2)
Thrombocytopenia	4 (19.0)	5 (25.0)
Serious	0 (0)	0 (0)
Leading to withdrawal of any treatment[b]	2 (50)	0 (0)
Tumor Lysis Syndrome	0 (0)	1 (5)
Serious	0 (0)	1 (5)
Leading to withdrawal of any treatment[b]	0 (0)	0 (0)

Data cutoff date: 2 July 2015; Percentages based on N.

[a] Defined based on grouped preferred terms (for definitions, see Section 5.5.6).

[b] Percentage based on the number of patients with at least one AE.

7.1.1.1 Infusion Related Reactions (IRR)

The most frequently observed ADRs in patients receiving obinutuzumab were IRRs which occurred predominantly during infusion of the first 1000 mg. In patients who received the combined measures for prevention of IRRs (adequate glucocorticoid, oral analgesic/anti-histamine, omission of antihypertensive medication in the morning of the first infusion, and the Cycle 1 Day 1 dose administered over 2 days), a decreased incidence of all grade IRRs was observed. The rates of Grade 3-4 IRRs (which were based on a relatively small number of patients) were similar before and after mitigation measures were implemented.

The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most patients having no IRRs during subsequent administrations of obinutuzumab. In the majority of patients, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g. anaphylaxis). Patients with a high tumor burden (i.e. high peripheral lymphocyte count in CLL [> 25 x 10^9/L]) may be at increased risk of severe IRR.

If the patient experiences an IRR, the infusion should be managed according to the grade of the reaction. For Grade 4 IRR, the infusion must be stopped and permanently discontinued. For Grade 3 IRR, the infusion should be temporarily interrupted and appropriate medication administered to treat the symptoms. For Grade 1–2 IRR, the infusion should be slowed down and symptoms treated as appropriate. Upon resolution of symptoms, infusion can be restarted, except following Grade 4 IRR, at no more than half the previous rate and, if the patient does not

experience the same adverse event with the same severity, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. If the previous infusion rate was not well tolerated, subsequent infusions should be adjusted per standard of care and institutional guidelines.

Patients should not receive further obinutuzumab infusions if they experience:

- acute life-threatening respiratory symptoms,
- a Grade 4 (i.e. life threatening) IRR or,
- a second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion).

Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Hypotension may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to, and throughout, each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication.

7.1.1.2 Hypersensitivity Reactions including Anaphylaxis

Hypersensitivity may be difficult to distinguish from infusion related reactions; however, anaphylaxis has been reported in patients treated with obinutuzumab. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped and treatment permanently discontinued. Patients with known IgE mediated hypersensitivity to obinutuzumab must not be treated (refer to *IB Section 6.2 Contraindications*).

7.1.1.3 Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS), including fatal TLS, has been reported with obinutuzumab. Patients who are considered to be at risk of TLS [e.g. patients with a high tumor burden or a high circulating lymphocyte count (> 25 x 10^9/L)] should receive adequate tumor lysis prophylaxis with uricostatics (e.g. allopurinol or adequate alternative) and hydration starting 12-24 hours prior to the infusion of obinutuzumab. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

7.1.1.4 Neutropenia

Severe and life threatening neutropenia including febrile neutropenia has been reported during treatment with obinutuzumab. Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. If treatment is necessary, it should be administered in accordance with local guidelines and administration of granulocyte colony-stimulating factors should be considered. Any signs of concomitant infection should be treated as appropriate. Cases of late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported.

7.1.1.5 Thrombocytopenia

Severe and life threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in Cycle 1 in patients treated with obinutuzumab.

Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of all concomitant therapies, which could possibly worsen

thrombocytopenia related events such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle.

7.1.1.6 Worsening of Pre-existing Cardiac Conditions

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

7.1.1.7 Infections

Obinutuzumab should not be administered in the presence of an active infection and caution should be exercised when considering the use of obinutuzumab in patients with a history of recurring or chronic infections. Serious, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported.

7.1.1.8 Hepatitis B reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including obinutuzumab (refer to IB).

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with obinutuzumab. At minimum this should include HBsAg-status and HBcAb- status. These can be complemented with other appropriate markers as per local guidelines. Patients with active Hepatitis B disease should not be treated with obinutuzumab. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation. Please refer to respective protocols for detailed guidance on this subject.

7.1.1.9 Progressive multifocal leukoencephalopathy (PML)

PML has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre- existing neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g. aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JCV DNA). Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

7.1.1.10 Immunization

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

7.1.1.11 The Obinutuzumab Adverse Events of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid

communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

- **The Obinutuzumab Events of Special Interest are:**
  - All TLS (irrespective of seriousness, causality or severity):
  - Secondary Malignancies

- Adverse events of special interest for this study include the following:
  - Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
    - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
  - Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

Figure 4. Summary of Deaths and AEs (Pooled Studies BO20999 and BO21003 Phase I/II)

	CLL Patients (N = 38)		NHL Patients (N =205)	
	Patients, n (%)		Patients, n (%)	
Death	13	(34.2)	61	(29.8)
AE leading to death	2	(5.3)	6	(2.9)
SAE	17	(44.7)	57	(27.8)
Grade 3 or 4 AE	30	(78.9)	85	(41.5)
Obinutuzumab-related Grade 3 or 4 AE	28	(73.6)	50	(24.3)
Obinutuzumab withdrawal due to AE	4	(10.5)	11	(5.3)
AEs of particular interest[a]				
Infusion-related reaction	38	(100)	169	(82.4)
Serious	10	(26.3)	11	(5.4)
Leading to obinutuzumab withdrawal[b]	3	(7.9)	3	(1.8)
Infection	21	(55.3)	98	(48)
Serious	4	(10.5)	14	(6.8)
Leading to obinutuzumab withdrawal[b]	0	(0)	1	(1.0)
Neutropenia	18	(47.4)	17	(8.3)
Serious	4	(10.5)	6	(2.9)
Leading to obinutuzumab withdrawal[b]	0	(0)	0	(0)
Thrombocytopenia	7	(18.4)	11	(5.4)
Serious	1	(2.6)	1	(0.5)
Leading to obinutuzumab withdrawal[b]	0	(0)	0	(0)
Tumor Lysis Syndrome	1	(2.6)	5	(2.4)
Serious	1	(2.6)	3	(1.5)
Leading to obinutuzumab withdrawal[b]	0	(0)	0	(0)
Gastrointestinal perforation	0	(0)	3	(1.5%)
Serious	0	(0)	3	(1.5%)
Leading to obinutuzumab withdrawal[b]	0	(0)	0	(0)

Excerpted from Table 31 of IB

Table 25 Summary of Deaths and Adverse Events in Patients with Relapsed/Refractory FL Treated with G-CHOP or G-FC (Study BO21000)

	Obinutuzumab + CHOP (N=28) n (%)	Obinutuzumab + FC (N=28) n (%)
Death	2 (7.1)	10 (35.7)
Death not due to disease progression	2 (7.1)	5 (17.8)
Related SAE	8 (28.6)	9 (25.0)
Grade 3 or 4 AE	20 (71.4)	24 (85.7)
Any treatment withdrawal due to AE	1(3.6)	9 (32.1)
AEs of particular interest[a]		
Infusion-related reaction	20 (71.4)	25 (89.2)
Serious	2 (7.1)	0 (0)
Leading to withdrawal of any treatment	0 (0)	0 (0)
Infection	26 (92.8)	23 (82.1)
Serious	7 (25.0)	9 (32.1)
Leading to withdrawal of any treatment	0 (0)	2 (7.1)
Neutropenia	14 (50.0)	18 (64.3)
Serious	4 (14.3)	5 (17.8)
Leading to withdrawal of any treatment	0 (0)	5 (17.8)
Thrombocytopenia	1 (4)	9 (25)
Serious	0 (0)	0 (0)
Leading to withdrawal of any treatment	0 (0)	0 (0)
Tumor Lysis Syndrome	0 (0)	0 (0)
Serious	0 (0)	0 (0)
Leading to withdrawal of any treatment	0 (0)	0 (0)
Patients Receiving Maintenance Treatment	**(N=23)**	**(N=17)**
SAE during maintenance	3 ()	6 ()
AE leading to withdrawal of any treatment	1 (4)	4 (24)
Grade 3 or 4 AE during maintenance	3 (13)	9 (53)
Post-maintenance Follow-up Period	**(N=23)**	**(N=17)**
SAE during post-maintenance follow-up	0 (0)	2 (12)

Results for both doses of obinutuzumab (400 mg and 1600/800 mg) were combined.
Data cutoff date: 2 July 2014.Percentages based on N.
[a] Defined based on grouped preferred terms (for definitions, see Section 5.5.5.2.4).

7.2 IBRUTINIB

Refer to Ibrutinib Package Insert/prescribing information for additional details.

To date, the most common adverse events seen with ibrutinib as a single agent include diarrhea, fatigue, nausea, cough, and peripheral edema. Grade 3 or higher adverse events were experienced by include neutropenia, thrombocytopenia, and anemia. Pneumonia was the most frequent nonhematologic Grade 3 or higher adverse event. The only serious events occurring in more than 2% of subjects were pneumonia, atrial fibrillation, and febrile neutropenia.

Combination studies with chemotherapy including bendamustine plus rituximab, fludarabine with rituximab, R-CHOP plus ibrutinib, as well as ofatumumab plus ibrutinib have also been reported. For these combination studies, the ibrutinib related toxicity profile was similar to that seen with single agent ibrutinib with diarrhea and nausea being the most frequent events followed by myelosuppression including neutropenia, anemia, and thrombocytopenia. The most common Grade 3 or higher adverse events in these combination studies were neutropenia, anemia, and thrombocytopenia, febrile neutropenia, and pneumonia.

Additional toxicities attributable to ibrutinib include atrial fibrillation as well as hemorrhagic AEs. The majority of the hemorrhagic adverse events were of Grade 1 or 2 in severity and include epistaxis and petechiae. Grade 3 or higher hemorrhagic AEs occurred at a low frequency (< 5%). Accordingly, although it is not entirely clear if this risk is due to ibrutinib, treatment with anticoagulants and anti-platelets must be evaluated closely.

Significant potential toxicities as defined by the package insert as captured by Lexicomp© are shown below.

Incidences combined for mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) unless otherwise specified.

7.2.1 IBRUTINIB AE OCCURRING >10%:

Cardiovascular: Peripheral edema (MCL: 35%, CLL: 23%), hypertension (CLL: 17%)
Central nervous system: Fatigue (MCL: 41%, CLL: 31%), dizziness (14% to 21%), headache (13% to 19%), chills (CLL: 13%)
Dermatologic: Skin rash (25% to 27%), skin infection (14% to 17%)
Endocrine & metabolic: Increased uric acid (38% to 40%; hyperuricemia >10 mg/dL: MCL 13%, CLL 4%), dehydration (MCL: 12%)
Gastrointestinal: Diarrhea (CLL: 63%, MCL: 51%), nausea (MCL: 31%, CLL: 21%), constipation (23% to 25%), abdominal pain (MCL: 24%, CLL: 15%), vomiting (19% to 23%), decreased appetite (17% to 21%), stomatitis (17% to 21%), dyspepsia (11% to 13%)
Genitourinary: Urinary tract infection (10% to 14%)
Hematologic & oncologic: Decreased platelet count (CLL: 71%, MCL: 57%; grades 3/4: 10% to 17%), bruise (CLL: 54% to 63%, MCL: 30% to 48%), neutropenia (47% to 54%; grades 3/4: 27% to 29%), decreased hemoglobin (41% to 44%; grades 3/4 MCL: 9%), petechia (11% to 17%)
Infection: Infection (grades 3/4: CLL 35%, MCL ≥25%)
Neuromuscular & skeletal: Musculoskeletal pain (MCL: 37%, CLL: 27%), arthralgia (CLL: 23%, MCL: 11%), muscle spasm (14% to 19%), weakness (13% to 14%)
Renal: Increased serum creatinine (≤1.5 x ULN: MCL 67%, CLL 23%; 1.5 to 3 x ULN: 4% to 9%)
Respiratory: Upper respiratory tract infection (CLL: 48%, MCL: 34%), dyspnea (MCL: 27%, CLL: 10%), sinusitis (13% to 21%), cough (19%), oropharyngeal pain (CLL: 15%), pneumonia (10% to 14%), epistaxis (MCL: 11%)
Miscellaneous: Fever (18% to 25%)

7.2.2 IBRUTINIB AE OCCURRING 1% TO 10%:

Cardiovascular: Atrial fibrillation (≥5%)
Central nervous system: Anxiety (CLL: 10%), insomnia (CLL: 10%), peripheral neuropathy (CLL: 10%)
Hematologic & oncologic: Malignant neoplasm (secondary; 5% to 10%; includes one death due to histiocytic sarcoma), anemia (MCL; grades 3/4: 9%), malignant neoplasm of skin (4% to 8%), hemorrhage (5% to 6%; grade 3 or higher bleeding events including subdural hematoma, ecchymosis, gastrointestinal bleeding, and hematuria), other carcinomas (1% to 2%)
Miscellaneous: Laceration (CLL: 10%)

7.3 ADVERSE EVENT CHARACTERISTICS

CTCAE term (AE description) and grade: The descriptions and grading scales found in the current NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site.
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE

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

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

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

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

Expectedness: Adverse Events can be 'Unexpected' or 'Expected.' Please see section **8.2.5** for definitions of Expectedness.

7.4 ATTRIBUTION OF THE AE

- Definite – the AE *is clearly related* to the study treatment.
- Probable – the AE *is likely related* to the study treatment.
- Possible – the AE *may be related* to the study treatment.
- Unlikely – the AE *is unlikely related* to the study treatment, but a causal relation cannot be completely excluded.
- Unrelated – the AE *is clearly NOT related* to the study treatment.

7.5 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems (UP) and Adverse Events (AE) will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site

All UP reports, including fatal and life-threatening events, must be reported to OHSU IRB within 5 business days after the PI learns of the event. If any of these require a change (as determined by the PI or the IRB) to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the OHSU IRB.

UP and AE reports are submitted through OHSU e- IRB and will be reviewed by OHSU IRB.

7.6 CENTRAL REPORTING OF ADVERSE EVENTS FOR MULTICENTER STUDIES:

The SAE/Unanticipated Problem reporting for multicenter investigator initiated clinical trials will follow the guidelines outlined in the OHSU Knight Cancer Institute Multi-Center Investigator Initiated Trials Coordinating Center Operations Manual.

A participating site must report an SAE to the to the institution's local IRB for action as required, as well as to the OHSU coordinating center study team by phone, fax, or email within 24 hours of learning of the event. The participating center will send the coordinating center materials regarding the SAE by completing and submitting FDA Form 3500, Voluntary reporting form as referenced in Section 7.5. The participating site should submit the following to OHSU to report an SAE:

- Redacted .pdf of submitted FDA Form 3500
- Investigator's judgment of attribution to study drug, obinutuzumab and/or study-driven procedures (should be included in form 3500A at time of report)
- CTCAE grade and name of the event (should be included in Form 3500A at time of report),
- Whether the investigator believes the event to be expected or unexpected based on the known risks of study drug and obinutuzumab
- Indication of whether the event will require follow up/ongoing
- All relevant source documentation related to the event, redacted

The OHSU coordinating center study team will review and submit SAEs to the FDA, OHSU IRB, and any other required contacts as required by the Knight Cancer Institute's Data Safety and Monitoring Plan. The principal investigator at the Coordinating Center is responsible for distributing IND and/or IDE Action Letters or Safety Reports, as applicable, to participating institutions for review and submission to their institution's local IRB.

And Oregon Health and Science University will be responsible for the distribution of safety information to Site IRB:

OHSU Institutional Review Board
3181 SW Sam Jackson Park Rd.
L106-RI
Portland, OR 97239
Phone# 503-494-7887

7.7 MEDWATCH REPORTING

For this investigator-initiated study, the investigator is the study sponsor. The investigator/sponsor is required to report adverse experiences to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse experiences to be reported include any unexpected (not listed in the package

label), serious adverse experiences with a suspected association to the study drug.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using the Form FDA 3500A MedWatch for Mandatory reporting. Please refer to section 8.5 for MedWatch reporting guidelines

When the serious adverse event is reported to the FDA, copies of the Form FDA 3500A MedWatch and supporting materials will be submitted to the OHSU Knight Cancer Institute and the IRB. A copy of the Form FDA 3500A MedWatch and supporting materials will be kept on file in the study regulatory binder.

7.8 REPORTING OF ADVERSE EVENTS TO GENENTECH

Obinutuzumab, as well as funding/support for this study is provided by Genentech. As such, additional reporting requirements are required as described in Section 8. Adverse events attributed as probable, possible and unlikely may generate queries to confirm causality and/or requests for additional information from the site.

8. REPORTING OF ADVERSE EVENTS

8.1 ASSESSMENT OF SAFETY

8.1.1 SPECIFICATION OF SAFETY VARIABLES

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to obinutuzumab per protocol, all events of death, and any study specific issue of concern.

8.1.2 ADVERSE EVENTS

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol- imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with Mantle Cell Lymphoma that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

8.1.3 SERIOUS ADVERSE EVENTS

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.

- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

8.1.4 Methods and Timing for Assessing AND Recording Safety variables

The investigator is responsible for ensuring that all AEs and SAEs, that are observed or reported during the study, are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

8.1.5 Adverse Event Reporting Period

The study period during which AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

8.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the obinutuzumab and/or ibrutinib (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the general guidelines in sections 8.1.7 and 8.1.8.

8.1.7 AEs Attributed to Obinutuzumab or Ibrutinib

There is a plausible temporal relationship between the onset of the AE and administration of obinutuzumab or ibrutinib, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the obinutuzumab or ibrutinib: and/or the AE abates or resolves upon discontinuation of the obinutuzumab or ibrutinib or dose reduction and, if applicable, reappears upon re-challenge.

8.1.8 AEs Not Attributed to Obinutuzumab or Ibrutinib

Evidence exists that the AE has an etiology other than the obinutuzumab or ibrutinib (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to obinutuzumab or ibrutinib (e.g., cancer diagnosed 2 days after first dose of study drug).

8.1.9 Expected and Unexpected AEs

Expected AEs are those AEs that are listed or characterized in the package insert or current IB.

Unexpected AEs are those not listed in the package insert or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the package insert or IB. For example, under this definition, hepatic necrosis would be unexpected if the package insert or IB only referred to elevated hepatic enzymes or hepatitis.

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

8.2 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

8.2.1 ELICITING ADVERSE EVENTS

A consistent methodology for eliciting AEs at all evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

8.2.2 SPECIFIC INSTRUCTIONS FOR RECORDING ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

8.2.2.1 Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

8.2.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

8.2.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

8.2.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions,
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

8.2.2.5 Pregnancy

If a female patient becomes pregnant while receiving obinutuzumab or within 18 months after the last dose of obinutuzumab, or the partner of a male patient becomes pregnant while receiving therapy or within three months of completing therapy, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to obinutuzumab should be reported as an SAE.

8.2.2.6 Post-Study Adverse Events

For studies involving extended follow up period, the investigator should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [including pregnancy occurring in the partner of a male study subject] who participated in the study that is believed to be related to prior exposure to obinutuzumab, after the end of the adverse event reporting period (defined as 30 days after the last dose of obinutuzumab).

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports

8.2.2.7 Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Oregon Health and Science University emailing Genentech a Quarterly line-listing documenting single case reports sent by Oregon Health and Science University to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Oregon Health and Science University to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

8.2.2.8 **EXGHANGE OF SINGLE CASE REPORTS**

Oregon Health and Science University will be responsible for collecting all protocol-defined Adverse Events (AEs), Special Situation Reports (including pregnancy reports) and Product Complaints originating from the Study for the Product.

The completed MedWatch form or Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints <u>*with*</u> an AE should be sent to:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation Reports and Product Complaints (with or without an AE), where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

SADR:
Serious AE reports that are related to obinutuzumab shall be transmitted to Genentech within 15 calendar days of the awareness Date.

Other SAEs
Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

AESIs
AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

Special Situation Reports

Pregnancy reports
While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients
Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 180 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

OTHER REPORTS

OHSU will forward a copy of the Final Study Report to Genentech upon completion of the Study.

8.3 OTHER SPECIAL SITUATION REPORTS

In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:

- Data related to the product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
  - In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

- **Product Complaints**

  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

8.4 MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
  Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

8.4.1 FOLLOW-UP INFORMATION

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

8.5.2 Additional Reporting Requirements for IND Holders:

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR §600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of obinutuzumab. An unexpected adverse event is one that is not already described in the obinutuzumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of obinutuzumab. An unexpected adverse event is one that is not already described in the obinutuzumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

AGGREGATE REPORTS

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech.

Copies of such reports should be emailed to Genentech at:

Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

REPORTING TO REGULATORY AUTHORITIES, ETHICS COMMITTEES AND INVESTIGATORS

Oregon Health and Science University, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

Oregon Health and Science University, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

Oregon Health and Science University will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

Oregon Health and Science University will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

8.5 STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Obinutuzumab (GA101) Protocols Email: ga101-gsur@gene.com Fax: 866-706-3927

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

8.7 QUERIES

Queries related to the Study will be answered by Oregon Health and Science University. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. Oregon Health and Science University agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

8.8 SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech shall have the final say and control over safety crisis management issues relating to the Product. Oregon Health and Science University agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech.

9. PHARMACEUTICAL AND/OR IMAGING AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

9.1 AGENT ACCOUNTABILITY

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent. In the case of this study which uses an FDA approved standard of care oral agent that is sent to the patient, we will aim to follow the guidelines as outlined in section 15.3 of the NCI investigator handbook. "Verification of Compliance" (https://ctep.cancer.gov/investigatorResources/docs/InvestigatorHandbook.pdf). Of note, in this setting it is recognized that for a SOC medication may be difficult and/or impractical to do an actual study drug inventory. Thus, we will document patient reporting of compliance with taking ibrutinib with the patient's drug diary.

9.1.1 OBINUTUZUMAB

9.1.1.1 Availability

Obinutuzumab is supplied to investigators by Genentech (South San Francisco, CA)

9.1.1.2 Product description

Obinutuzumab is provided as a single 1000 mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50 mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188 and highly purified water (HPW).

9.1.1.3 Storage requirements

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For clinical formulation-specific and batch-specific instructions, and information on in-use stability, see the packaging label.

9.1.1.4 Stability

Stable in Normal Saline

9.1.1.5 Route of administration

Infusion as noted in Section 5.1.1

9.1.2 IBRUTINIB

Ibrutinib will be provided per standard of care (as a commercial agent). Details of its administration are listed in Section 5.1.

10. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Details and background regarding correlative studies are described in Section 2.4. Correlative studies include Gene Expression Profiling using the nanostring platform, sequencing of specific lymphoid genes using the ion torrent platform, BTK and PLCγ mutations, and MRD testing using flow cytometry and next generation sequencing.

In order to participate in this study, all subjects must agree to assessment of tumor tissues for correlatives. Every attempt should be made to obtain tissue immediately prior to on study treatment. However, in the event fresh tissue is not available, archival tissue may be used. Additional biopsies to assess for mechanisms of resistance should be obtained at the time of disease progression. Tissue sources can include lymph nodes, extranodal sites, or bone marrow.

Specimens collected for correlative studies will be stored at OHSUBatch testing of the specimens will be conducted either periodically throughout the study or at the end. The specimens will be used for this research study only and not made available for future unspecified research. Specimens will be assigned a code number and only the sponsor-investigator and designated investigators and study staff involved in the conduct of the study will be authorized to link the code number to a subject.

10.1 COLLECTION OF SPECIMENS

Additional details of testing performed is available in Section 2.6 and further outlined below.

In addition to standard pathology testing, samples for correlative studies will be obtained as follows:

1) Screening:
    a. Nodal Tissue: Fresh or archival tumor tissue will be collected for gene expression profiling and targeted sequencing including BTK mutations.
    b. Bone Marrow: 5 mL of fresh bone marrow aspirate in EDTA tube or heparinized syringe.
    c. Peripheral Blood: 5 mL EDTA or citrate tube.
2) Post Induction/on Treatment:
    a. If patient is in CR: Bone Marrow: 5-7 mL or Bone Marrow aspirate in a EDTA tube for MRD testing by flow cytometry. 1-2 mL of this sample is to be placed in a separate EDTA tube for evaluation by next gen sequencing.
3) Disease Progression:
    a. Nodal Tissue: Fresh tumor tissue will be collected for gene expression profiling and targeted sequencing including BTK mutations.
    b. Bone Marrow: 5 mL of fresh bone marrow aspirate in EDTA tube or heparinized syringe.

Blood samples and bone marrow aspirates collected at OHSU will be transported to Dr. Spurgeon's laboratory within 2 hours after collection. Samples will be transported at room temperature. Blood samples collected at participating sites will be shipped ambient to Dr. Spurgeon's laboratory the day of collection. Sample shipments from participating sites can only be accepted at Dr. Spurgeon's lab Monday-Friday. Prior to shipping, timing of the shipment should be coordinated with the OHSU study team.

Shipping Address:

Spurgeon Lab
Oregon Health & Science University, Knight Cancer Institute
Knight Cancer Research Building
Dock 61, Room 2141
2720 SW Moody Ave
Portland, OR 97201

Samples for standard MRD testing via flow cytometry will be performed at the treating institution. OHSU MRD testing will be performed at OHSU pathology. For non-OHSU participants, this can be performed per standard of care at the treating institution.

10.2 GENE EXPRESSION PROFILING (GEP)

Formalin fixed, paraffin embedded MCL tissue biopsies or lysates from 10^4 lymphoma cells. Reports will be generated by hematopathology through the OHSU system.

10.2.1 SEQUENCING USING ION TORRENT PLATFORM AND EVALUATING BTK MUTATIONS

Specimen Requirements include: Peripheral blood: 5 mL EDTA (lavender top tube) or 5 mL Citrate tube or Bone marrow aspirate: 5 mL in EDTA (lavender top tube) or a paraffin block or 10 unstained sections of a bone marrow or lymph node biopsy (4-5 microns). DNA will be isolated using QIAamp isolation kit (QIAGEN). Sequencing will be performed by the Knight Diagnostic Lab (KDL).

10.3 MRD TESTING

MRD testing should be performed according to institutional standards. Samples may be assessed at each investigative subsite or shipped to lead site (OHSU) for processing. For all samples processed at OHSU, 5-7 ml of bone marrow aspirate in a heparinized syringe should be sent refrigerated for MRD flow cytometry analysis. 1 ml will be frozen for possible MRD testing by next gen sequencing. Samples should be shipped to:

Hematopathology Division, Mailcode L471
Surgical Pathology Office
Department of Pathology
Oregon Health & Sciences University
3181 SW Sam Jackson Park Road
Portland, OR 97239

Surgical Pathology Office # is (503) 494-6776

11. STUDY PROCEDURES AND SCHEDULE OF EVENTS

11.1 SCREENING/BASELINE VISIT

Baseline screening evaluations are to be conducted within 4 weeks prior to start of protocol treatment. Refer to Section 11.6 and Table 3 for more detailed description of study procedures.

11.2 STUDY VISITS

Subjects will be followed until disease progression. Subjects removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. The schedule of events, Tables 3-4, lists the mandatory data collected at each time point for the clinical trial but it is expected that additional tests/procedures or visits may occur as standard of care, which is entirely at the discretion of the investigator. Most patients will have additional laboratory studies and clinical evaluations outside of this schedule as part of their standard of care. Every effort will be made to adhere to the schedule as close as possible. This is the minimum schedule of laboratory studies and follow-up visits required for the study.

11.3 END OF TREATMENT - OBINUTUZUMAB

Subjects will be evaluated 1 month (28 days) ±7 days after completion of obinutuzumab maintenance for End of Treatment procedures. Every attempt will be made to devise a treatment plan weeks before the patient stops Obinutuzumab. In the case where the patient withdraws from the study abruptly for any reason, a standard of care treatment plan will be formulated as soon as possible. Subjects will be encouraged to return for the follow- up visit.

11.4 FOLLOW-UP VISIT

After completion of maintenance obinutuzumab (up to 2 years of maintenance) patients will be continued on ibrutinib per standard of care. Follow up will be performed per standard of care and patients will be followed until disease progression or death. No planned study follow up is mandated. However, every 6 months, patients and/or patient records may be queried for progression and survival status for up to 3 years. The PI may terminate the study prior to 5 years; however, after 5 years, the study must be terminated.

11.5 STUDY ASSESSMENTS AND PROCEDURES

Dose adjustments or the occurrence of hematologic or non-hematologic grade 3 or 4 adverse events may require additional clinical evaluations and/or laboratory studies but should not be any less frequent than the schedule outlined.

- **Demographics and Medical History**: Demographics and a complete medical history will be collected at visits prior to starting study treatment.

- **Concomitant Medications**: All concomitant medications and treatments must be recorded in the case report form (CRF). Any prior medication received up to 30 days prior to the Screening visit will be recorded in the CRF. Concomitant treatments that are required to manage a subject's medical condition during the study will also be recorded in the CRF. Prior and/or ongoing medications will be reviewed during screening to determine subject eligibility. The medication record will be maintained following enrollment including any changes to the dose or regimen. Prior and concomitant mediation including any prescription, over the counter or natural/herbal/multivitamin preparations taken will be recorded.

- **Physical Exam**: The physical exam at Screening should include weight, vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation), and a detailed exam of lymph nodes as well as liver and spleen.

- **Targeted Physical Exam**: Physical exam to include heart, lungs, abdomen, lymph nodes and lower extremities.

- **Performance Status**: ECOG will be determined and performed at the visits indicated in the schedule of events.

- **Nursing Assessment**: Standard nursing assessment performed by chemotherapy certified infusion nurses prior to drug administration. Assessment should include study drug diary review of ibrutinib self-administration.

- **Pregnancy Test**: A urine pregnancy test is required for all female subjects during screening for women of childbearing potential. If the urine pregnancy test is positive, serum pregnancy tests must be performed per institutional standards.

- **Weight**: Must be collected at each study visit.

- **Height**: Must be collected prior to day of study treatment and at additional visits as defined on Study Visit table.

- **Vital Signs**: Vital sign measurements should be taken per institutional standards at each study visit.

- **Laboratories**: The following labs will be collected as outlined in Table 3:
  - Complete Blood Count (CBC): Should include a 5 point differential (CBC w/ diff.), including, at a minimum: white cell count, hematocrit, hemoglobin, absolute neutrophil count, absolute lymphocyte

count, and platelet count.
  - Complete Metabolic Panel (CMP): Should include, at a minimum, creatinine, K, Na, total bilirubin, albumin, AST, ALT, Ca, ALP, phosphorous, glucose, uric acid, LDH (point of care labs acceptable), and BUN.
  - beta-2 microglobulin (B2M)
  - Hepatitis B surface antigen (sAg)
  - Hepatitis B core antibody (cAb)
  - Immunoglobulin G (IgG)
  - Uric acid

- **FDG-PET**: Should be performed at baseline and at the end of cycle 6. Additional scans will be done per standard of care if, as assessed by the investigator, the subject may have had CR.

- **Imaging**: Subjects should undergo staging (and restaging) CT scans with IV contrast including neck (if involved at baseline), chest, abdomen, and pelvis. MRI of these areas may be substituted for CT scan if the subject a) refuses CT or b) has contraindications to IV contrast i.e. allergy. Imaging will be performed at baseline, prior to cycle 3 initiation, end of cycle 6 and Q 4 months (± 7 days) while on obinutuzumab maintenance. Index lesions will be followed from baseline.

- **Bone Marrow Aspirate and Biopsy**: Will be performed at baseline and at the end of cycle 6 if involved at baseline. Additional marrow is required after attaining a CR by imaging studies. IHC including cyclin D1 staining, flow cytometry for MRD, and FISH including t (11, 14). If found to be MRD negative, next gene sequencing will be performed to confirm.

- **Optional Lymph Node Fine Needle Aspiration:** For Correlative Studies for gene expression profiling and sequencing. Subjects must provide explicit consent to participate in this optional specimen collection. A second lymph node fine needle aspiration will be collected at baseline and upon disease progression, if applicable.

- **Peripheral Blood**: Collected at baseline and disease progression. For Correlative Studies for gene expression profiling and sequencing.

- **Adverse Event assessments**: Toxicities and adverse experiences will be assessed at each visit using the NCI Common Toxicity Criteria for Adverse Events 4.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.6 SCHEDULE OF EVENTS

Table 3. INDUCTION SCHEDULE: Screening/Baseline, Cycles 1 through 6, and End of Induction							
Visit	Screening/ Baseline	Cycle 1	Cycle 1	Cycle 1	Cycles 2-6	End of Induction	End of Induction[1]
Day		Day 1	Day 8	Day 15	Day 1	Day 28	Day 56
Window	- 28 days of C1D1					±7 days	±7 days
Performance Status	X	X			X	X	
Complete Physical	X	X			X		
Targeted physical exam			X				
RN assessment		X		X	X	X	
Height	X					X	
Vital signs (heart rate, BP, RR, O2)	X	X	X	X	X	X	
CBC w/differential[2]	X	X	X	X	X	X	X
Chemistry panel (CMP)	X	X	X	X	x**4**	x**4**	
LDH	X	X	X	X	X	X	
Uric Acid	X		X	X	X	X	
Urine or β-hCG pregnancy test[3]	X						
Beta-2 microglobulin	X						
Hepatitis B surface antigen (sAg)	X						
Hepatitis B core antibody (cAb)	X						
Immunoglobulin G (IgG)	X						
CT and PET with contrast (neck, chest, abdomen and pelvis)[5]	X				x**6**	X	
Bone Marrow Aspirate with Biopsy (IHC including cyclin D1 staining, flow cytometry, and FISH including t (11,14)	X						x**7**
OPTIONAL: Lymph node fine needle aspiration or biopsy	x8						
5 mL peripheral blood	X						X
Obinutuzumab IV administration		X	X	X	X		
Ibrutinib PO administration		Daily starting at Cycle 1 Day 1					
Ibrutinib drug diary		Daily starting at Cycle 1 Day 1					
Ibrutinib drug diary review					X	X	X
AE Assessment		X	X	X	X	X	X

KEY:
[1]Visit may be combined with the first maintenance infusion visit but bone marrow biopsy must be performed prior to the first dose of obinutuzumab maintenance.
[2] If a Grade 3 hematologic DLT occurs, repeat CBC 2x/month (Day 1 and Day 15) will be performed. If Grade 4 hematologic DLT occurs, repeat CBC weekly until toxicity resolves to < Grade 2.
[3]For women of childbearing potential only
[4]May be performed as Basic Metabolic Panel plus (BMP +) or as point of care chemistry panel
[5]MRI of these areas may be substituted for CT scan if the subject a) refuses CT or b) has contraindications to IV contrast i.e. allergy.
[6] Prior to Cycle 3 drug initiation (a window of 7 days prior to C3D1)
[7] End of Cycle 6 bone marrow biopsy will be done only in participants with initial bone marrow involvement. If found to be MRD negative, gene sequencing will then be performed to confirm.
[8]Additional fine needle aspiration will be collected upon disease progression, for subjects for whom this applies.

Table 4. MAINTENANCE SCHEDULE: Visits 1 through 12 and End of Study Visit

Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	End of Study
Day	Day 56	Day 112	Day 168	Day 224	Day 280	Day 336	Day 392	Day 448	Day 504	Day 560	Day 616	Day 672	Day 700
Window	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (heart rate, BP, RR, O2)	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/diff[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP [2]	X	X	X	X	X	X	X	X	X	X	X	X	X

LDH	X	X	X	X	X	X	X	X	X	X	X	X	X
Uric Acid	X	X	X	X	X	X	X	X	X	X	X	X	
CT and PET with contrast (neck, chest, abdomen and pelvis)[3]		X		X		X		X		X		X	
Obinutuzumab IV administration	X	X	X	X	X	X	X	X	X	X	X	X	
Ibrutinib PO administration	Daily												
Ibrutinib drug diary	Daily												
Ibrutinib drug diary review	X	X	X	X	X	X	X	X	X	X	X	X	
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	

KEY:

[1] If a Grade 3 hematologic DLT occurs, repeat CBC 2x/month (Day 1 and Day 15) will be performed. If Grade 4 hematologic DLT occurs, repeat CBC weekly until toxicity resolves to < Grade 2.

[2] May be performed as Basic Metabolic Panel plus (BMP +) or as point of care chemistry panel

[3]Imaging to be performed every 4 months (+ or – 7 days) while on obinutuzumab maintenance. MRI of these areas may be substituted for CT scan if the subject a) refuses CT or b) has contraindications to IV contrast i.e. allergy. A PET scan should be performed per standard of care if in the eyes of the investigator, the subject may have had a CR.

Table 5. FOLLOW UP SCHEDULE: Every 6 months for 3 years

Month	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
Disease Status	X	X	X	X	X	X
Survival Status	X	X	X	X	X	X

12. MEASUREMENT OF EFFECT

The primary objective of this study is best overall response of CR/PR and secondary objectives will include progression free survival (PFS) and toxicity.

12.1 BEST OVERALL RESPONSE

Subjects who received both study medications and have had one response assessment (first radiologic response assessment takes place after cycle 2) will be evaluable for Best Overall Response. Patients who progress prior to the initial planned radiologic evaluation will be defined as having progressive disease and go off study. Diagnostic CT and PET will be used to measure response. Progression must be confirmed by imaging.

12.1.1 TARGET LESIONS/MEASURABLE DISEASE

Subjects must have at least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma. Up to six of the largest dominant nodes or tumor masses should be selected. If possible, these should be from different body regions and whenever possible, should include mediastinal and retroperitoneal disease sites. The site of disease must be greater than 1.5 cm in the long axis regardless of short axis measurement or greater than 1.0 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions. Extranodal sites can be included and for extranodal sites in the liver or spleen, these must measure at least 1.0 cm in the two greatest dimensions.

12.1.2 EVALUABLE NON-TARGETED DISEASE RESPONSE

Subjects who have lesions present at baseline that do not meet the size criteria to be considered measurable disease, have received at least two cycles of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease response. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2 RESPONSE CRITERIA

Response to therapy will be assessed per the Lugano criteria[28]. Pre-treatment evaluations include FDG-PET and diagnostic CT as outlined. Best overall response (PR or CR) as per Section 12.3.1 will be evaluated throughout the study and used to inform the primary endpoint. Only patients achieving a PR or greater after induction (the first 6 cycles of treatment) are eligible for ongoing therapy. Therefore, prior to proceeding with maintenance therapy (ie after cycle 6), best overall response (PR or CR) will be documented by PI. Subjects with a PR or greater are eligible to continue with ibrutinib plus obinutuzumab maintenance.

For FDG-PET response **Deauville criteria** will also be used in conjunction with CT as described below to assign PR or CR**.**

The Deauville scale ranges from 1 to 5, where 1 is best and 5 is the worst. Each FDG- avid (or previously FDG-avid) lesion is rated independently.

1) no uptake or no residual uptake (when used interim)
2) slight uptake, but below blood pool (mediastinum)
3) uptake above mediastinal, but below or equal to uptake in the liver
4) uptake slightly to moderately higher than liver
5) markedly increased uptake or any new lesion (on response evaluation)

12.3 RESPONSE ASSESSMENT

Imaging Response Assessment using Deauville Criteria

Complete response (CR): scores 1, 2 or 3 together with absence of FDG-avid bone marrow lesion(s) are interpreted as complete metabolic response (CR), irrespective of a persistent mass on CT

Partial response (PR): a Deauville score of 4 or 5, provided:

- uptake is decreased compared with baseline and
- absence of structural progression development on CT

Stable disease (SD): also called no metabolic response: a Deauville score of 4 or 5 without significant change in FDG uptake from baseline.

Progressive disease (PD): a Deauville score of 4 to 5 with increasing intensity compared to baseline or any interim scan and/or any new FDG-avid focus consistent with malignant lymphoma.

12.3.1 BEST OVERALL RESPONSE

Determined by evaluation of measurable and non-measurable disease as well as marrow evaluation as outlined below

12.3.1.1 Complete Response (CR)

Complete disappearance of all detectable clinical evidence of disease and disease- related symptoms if present prior to therapy. Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when

1) the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, the designation of CR requires all nodal indicator lesions to regress to the size of normal lymph nodes. Lymph nodes that were > 15 mm in GTD regardless of the short axis diameter at the screening tumor assessment must regress to ≤ 15 mm in GTD regardless of the short axis diameter. Lymph nodes that were 11 to 15 mm in GTD and > 10 mm in the short axis diameter at the screening tumor assessment must regress to ≤ 10 mm in the short axis diameter.
2) The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
3) If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (> 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

12.3.1.2 Partial Remission (PR)

1) ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; (b) if possible they should be from disparate regions of the body; (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2) No increase in the size of the other nodes, liver, or spleen.

3) Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4) With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5) Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
6) No new sites of disease should be observed (e.g., nodes > 1.5 cm in any axis).
7) Typically, FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8) Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

12.3.1.3 Stable Disease (SD)

Failing to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see below).

Typically, FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post- treatment CT or PET.

Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD; after CR) or Progressive Disease (PD; for Patients with PR or SD)

12.3.1.4 Progressive/Relapsed Disease

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1−1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities

1) At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or more than 1.5 cm in the long axis.
2) At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
3) Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 15 mm in its long axis by CT).

4) Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease.

Notes: Bone marrow status is evaluated as follows:
Positive: Unequivocal cytological or architectural evidence of malignancy. Negative: No aggregates or only a few well-circumscribed lymphoid aggregates.

12.3.2 EVALUATION OF BEST OVERALL RESPONSE

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

12.4 PROGRESSION FREE SURVIVAL

Progression Free Survival (PFS) is defined as the time from the first day of combined study treatment (obinutuzumab plus ibrutinib -Day 1 of Cycle 1) to disease progression or death, whichever occurs first. If a patient has not experienced progressive disease or death, PFS will be censored at the day of the last tumor assessment or Cycle 1, Day 1 if no post-baseline tumor assessment.

12.5 EVALUATION OF TOXICITY

All subjects will be evaluable for toxicity from the time of their first treatment with *obinutuzumab* (Day 1 of Cycle 1) and through 30 days after completion of on-study therapy (either combination or single agent ibrutinib). Toxicity event will be classified according to the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Adverse events collection will begin at first administration of one or both study drugs.

12.6 METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

PET: A positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology. In order to make this assessment, potential PET avid areas must be compared to mediastinal and liver blood pools. For splenic lesions, uptake must be greater than surrounding liver and spleen. PET will NOT be used to measure marrow disease.

13. DATA REPORTING AND REGULATORY REQUIREMENTS

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system stored on REDCap CLOUD secure servers, which facilitates information being stored in a unified format and location. REDCap Cloud is a web-hosted application hosted by nPhase (located in Encinitas, California), and is an approved system that has been reviewed by OHSU Security. To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and dates associated with patient's medical care and life events. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Data from correlative studies will be entered into the EDC system by study personnel at OHSU. All other electronic data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data.

Quality assurance will be conducted as outlined in section 13.7 under data safety and monitoring.

13.1 MULTICENTER GUIDELINES

Collaborating research subsites may be invited to participate in this study. In such cases, OHSU will serve as the coordinating center and will manage trial data in the following ways:

a. Confirm that all sites have received and are using the most recent version of the protocol. The protocol must not be rewritten or modified by anyone other than the OHSU Investigator. Documentation of the version that was sent to the site must be kept in the regulatory binders.
b. Confirm that the protocol and informed consent form have local IRB approval at each site prior to registration of the first participant. Documentation of IRB approval from other sites for continuing review must be submitted and kept in the binder.
c. Provide centralized participant registration in the clinical research management system.
d. Ensure collection and review of applicable source documents and case reports by the OHSU Investigator to ensure protocol compliance.
e. Maintain documentation for all SAE reports and submit regular summaries of all AEs, SAEs and UPs from all sites to the Knight DSMC per DSMC requirements.
f. Ensure that relevant IRB correspondence and study status changes are communicated to all participating sites within 5 business days. Any changes that affect participant safety of study enrollments will be communicated immediately.
g. Submit documentation to the FDA such as protocol amendments, annual reports, and safety reports for unexpected, fatal or life-threatening events that are associated with the use of the investigational product.
h. Participating sites must submit regulatory documents including, but not limited to the following:
    - Current CV (signed and dated) for each Investigator.
    - Current medical license number for physician investigators.
    - Current signed FDA Form 1572.
    - Certificate of completion of institution-required human participant training course, the NIH online training in the protection of human research participants or other appropriate training.
    - Documentation of institutional Conflict of Interest.

i. IRB-approved site-specific ICF (must be reviewed and approved by OHSU Investigator and study team prior to submission to the local IRB.
j. All IRB-approved documents and approval memos.
k. Site delegation of authority and signature log.
l. Site DSMP.
m. Completed CRFs (data entry) within 10 business days of study visit.

13.2 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (CI) Clinical Research Review Committee (CRRC) and the OHSU Institutional Review Board (IRB) prior to any subject being consented on this study.

13.3 INFORMED CONSENT

Written informed consent will be obtained from all subjects, or the legally authorized representative of the subject, participating in this trial, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. If a subject's signature cannot be obtained, and for all subjects under the age of 18, the investigator must ensure that the informed consent is signed by the subject's legally authorized representative.

Documentation of the consent process and a copy of the signed consent shall be maintained in the subject's medical record.

COVID-19 Modified Procedures

In the event of an initial consent or a re-consent (due to a protocol amendment or an updated investigator's brochure, or any other change to the Informed Consent Form where the participants must be informed) where COVID-19 restrictions prevent the participant from consenting in person at the clinic, the participant will be emailed, faxed, or mailed the new consent or the revised consent and a phone call will take place between the consenting staff member, the participant and an impartial witness. An impartial witness is involved when the participant is not able to return the signed page for documentation of consent. The witness will be able to hear both sides of the conversation and attest to the subject's decision to participate. If an impartial witness is not available, a recording of the conference call can be used in place of the witness. The recording will be used as documentation and will be kept in the trial records.
The consent form or any changes to the consent form for a re-consent will be explained in detail and the participant will be given time to ask any questions. The staff member will ask questions to gauge understanding. Once all questions have been addressed, the participant will be instructed to sign and date the consent. The consent form will then be mailed, faxed, or scanned and emailed, in its entirety to the study site. The conversation and signing of the consent is then documented in the participant's records. Upon receipt of the signed consent, the consenting staff member who performed the phone consent will sign and date the consent and document in the participant's records. Copies of fully-executed consent forms (i.e. signed by participant and site personnel) will be provided to participants. MyChart may be used to collect study consents remotely.
Research participant visits will be conducted remotely whenever possible during the COVID-19 outbreak. On-site visits will be limited to visits that are "essential to the health and/or well-being" of our subjects. Participants may have procedures done locally, assessments conducted over the phone, or procedures may be skipped or performed outside of window depending on the PI assessment of what is essential to the health and well-being of the participant. Every participant will be considered on a case by case basis by the PI and the study team. Decisions will be documented by the study team.
Participants will be informed of the modified procedures by phone or at a visit and their verbal agreement noted. All deviations from the protocol will be logged and its relation to the COVID-19 restrictions will be noted. Additionally, site-monitoring visits may be conducted remotely or postponed during this time.
Consenting, re-consenting and participant visits will be followed per work instructions developed at OHSU.

13.4 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the subject. In that event, the investigator must notify the CRRC and IRB in writing within 10 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol.

13.5 MAINTENANCE OF RECORDS

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Trials Office. Records must be maintained according to sponsor or FDA requirements.

13.6 OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

13.7 OHSU KNIGHT CANCER INSTITUTE DATA AND SAFETY MONITORING PLAN

In addition to complete study and pharmacy files, complete records must be maintained on each subject treated on this protocol. OHSU Knight Cancer Institute, through the auditing function of the Knight Clinical Trials Office, is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies and in accordance with the Data and Safety Monitoring Plan policies and procedures here.

Locally initiated studies will be audited by OHSU Knight CI Auditor. Newly approved studies may be audited any time after enrollment has been initiated. Each OHSU Knight approved treatment protocol will be audited on an annual basis in accordance with the Knight Data and Safety Monitoring Plan.

13.8 INCLUSION OF WOMEN, MINORITIES AND CHILDREN

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied. The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon (**Table 6** and **Table 7**).

Table 6. Population Demographics - Oregon (%)

Ethnic Category	**Sex/Gender**		
	Females	Males	Total
Hispanic or Latino	5.9	5.8	11.7
Not Hispanic or Latino	44.5	43.8	88.3
Ethnic Category: Total of all subjects*	50.4	49.3	100*
Racial Category			
American Indian or Alaskan Native	0.7	0.7	1.4

Asian	1.9	1.8	3.7
Black or African American	0.9	0.9	1.8
Native Hawaiian or other Pacific Islander	0.2	0.1	0.3
White	42.1	41.5	83.6
More than one race	1.9	1.9	3.8
Unknown/Other	2.7	2.6	5.3
Racial Category: Total of all subjects*	50.4	49.5	100*
TOTALS	50.4	49.6	100*
Source: U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.			

Table 7. Projected Accrual for the Present Study

Ethnic Category	**Sex/Gender**			
	Females	Males	Unknown	Total
Hispanic or Latino	1	1	0-1	2
Not Hispanic or Latino	9	9	0-1	18
Unknown	0-1	0-1	0-1	0-1
Ethnic Category: Total of all subjects*	10	10	0-1	20
Racial Category				
American Indian or Alaskan Native	0-1	0-1	0-1	0-1
Asian	0-1	0-1	0-1	1
Black or African American	0-1	0-1	0-1	0-1
Ethnic Category	**Sex/Gender**			
	Females	Males	Unknown	Total
Native Hawaiian or other Pacific Islander	0-1	0-1	0-1	0-1
White	8	8	0-1	20
More than one race	0-1	0-1	0-1	1
Unknown	1	1	0-1	1
Racial Category: Total of all subjects*	10	10	0-1	20
Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.				

13.9 INCLUSION OF CHILDREN

This protocol does not include children for the following reasons:

1) The number of children with this type of cancer is limited.
2) No dosing or adverse event data are currently available on the use of this study agent in this way in subjects <18 years of age, therefore, children are excluded from this study.

14. STATISTICAL CONSIDERATIONS

14.1 STUDY DESIGN

This is a single-arm two-stage phase II trial combining obinutuzumab and ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma. It is designed according to Simon's optimum two-stage design, and a total of 20 patients will be enrolled at OHSU. In Stage I, 6 patients are enrolled, and if there are 3 or fewer responses (CR/PR), the trial will be closed. Otherwise the trial will continue until 20 patients are enrolled. The treatment is considered unworthy of further investigation if 14 or fewer respond. Of note, this study will use two already FDA approved agents-obinutuzumab is FDA approved for chronic lymphocytic leukemia, not MCL, and ibrutinib is FDA approved for relapsed/refractory MCL as a single agent.

14.2 PRIMARY AND SECONDARY ENDPOINTS

14.2.1 PRIMARY ENDPOINT

Best overall response of CR/PR as defined in Section 12.1.

14.2.2 SECONDARY ENDPOINTS

Toxicity is defined as any adverse event grade 3 or higher, defined in Sections 5 and 6. Progression free survival is defined in Section 12.1.3.

14.2.3 EXPLORATORY AND CORRELATIVE ENDPOINTS

1. Gene expression profiling using Lymph5Cx test
2. Sequencing using the ion torrent platform (for MRD and known mutations in lymphoma)
3. Sequencing of BTK and PLC□2 to evaluate for BTK and PLC□2 mutations
4. MRD by flow cytometry and next generation sequencing post treatment

14.3 ANALYSIS POPULATIONS

An evaluable patient set consists of those who receive at least one dose of both drugs (obinutuzumab and ibrutinib). A per protocol patient set consists of those who receive at least 2-cycles of combined therapy. Primary and secondary endpoints will be assessed using the evaluable patient set as well as the per-protocol patient set. Progression must be confirmed radiologically. Patients progressing (PD) prior to the first scheduled response assessment of measurable disease will be counted as non-responding patients. Evaluable patients who do not have response assessments (e.g. are removed for toxicity) will also be counted as non-responding patients. Safety analysis will include all subjects receiving at least one dose of obinutuzumab and ibrutinib. Ibrutinib treatment may be interrupted for 14 days. If ibrutinib is held > 14 days, patients are allowed to stay on study and are evaluable for response if they have completed at least 2 cycles (56 days) of combination therapy.

14.4 STATISTICAL ANALYSIS PLAN

A treatment is considered not worthy of further investigation if 14 or fewer responses are observed among 20 patients. Phase II data will be used to provide evidence of anti- tumor activities. We will provide a point and interval estimate (95% confidence interval) of the overall response (CR/PR). Kaplan-Meier method will be used to estimate progression-free survival (PFS). For exploratory analyses, a logrank test will be used to compare PFS between patients with and without MRD negativity after induction (obinutuzumab plus ibrutinib) treatment. A Fisher's exact test will be used to compare the best overall response between patients with and without BTK or PLCγ2 mutations.

14.4.1 INTERIM ANALYSES AND STOPPING RULES

This trial is designed according to Simon's two-stage optimal design. The primary endpoint of the best overall response is the best response recorded from the start of the treatment until disease progression (section 12.1). For

the purpose of the interim analysis, we will use the best response achieved during the first six months. *After Stage I enrollment of 6 patients, an interim analysis of the response (CR/PR) within the first six months of treatment will be conducted. If there are 3 or fewer responses (CR/PR) among 6 patients, the trial will be closed due to futility. Stage II will enroll additional 14 patients. After completion of Stage II a final analysis will be conducted to determine the best overall response rate defined in 12.1. If 14 or fewer responses, this combination will not be deemed worthy of additional investigation.

There are two safety stopping rules in this trial. Sequential boundaries are constructed based on the method by Ivanova et al[32]. Specifically the accrual will be suspended if excessive numbers of DLT events (as defined in Section 5.10) are observed, that is, if the number of DLT is equal to or exceeds *bn* out of *n* patients with full follow-up (see Table 8 for Grade 4+ DLTs and Table 9 for Grade 3+ DLTs). The boundary is equivalent to testing the null hypothesis that, after each patient, that the event rate is significantly higher than 20% (Table 8: Grade 4+ DLTs) and 33% (Table 9: Grade 3+ DLTs) using one-sided 10% significance level.

Table 8. Sequential boundary and stopping rule for Grade 4 or higher DLTs: suspend the accrual if there are *bn* or higher events out of *n* patients.

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, *bn*	-	2	3	3	3	3	4	4	4	5	5	5	6	6	6	6	7	7	7	7

Table 9. Sequential boundary and stopping rule for Grade 3 or higher DLTs: suspend the accrual if there are *bn* or higher events out of *n* patients.

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, *bn*	-	-	3	4	4	4	5	5	6	6	7	7	8	8	8	9	9	10	10	10

**Please note: As of May 11, 2018, seven patients were enrolled in the Stage I portion of the study with one patient withdrawing a consent prior to the initial response assessment. Of six evaluable patients, five responses (3 CR and 2 PR) were observed. Therefore, the trial passed the Stage I futility criteria (stop if 3 or fewer responses out of 6), and it is currently in the Stage II portion of the study. Further, there were 2 patients with Grade 3 or higher DLT events and 1 patient with Grade 4 or higher DLT events among seven patients exposed to the study drugs. Therefore, the toxicity boundaries were not crossed, and the treatment is considered safe to continue.*

14.4.2 SAMPLE SIZE AND POWER

Patients treated on the Pivotal ibrutinib trial with relapsed/refractory mantle cell lymphoma had achieved the best overall response rate (CR/PR) of 68%. Treatment of relapsed MCL with obinutuzumab resulted in a CR/PR response rate of 27%. Therefore, based on one- sided 5% significance and 90% power using a control response rate of 55% vs. an experimental response rate (obinutuzumab plus ibrutinib) of 85% and Simon's two-stage optimum design, 20 subjects will need to be enrolled. Stage I will enroll 6 subjects, and if there are 3 or fewer responses (CR/PR), the trial will be closed due to futility. Otherwise, Stage II will enroll additional 14 patients with the total sample size of 20 patients.

14.5 HANDLING OF MISSING DATA

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. The labs or studies outlined in the schedule of events may be completed within 7 days of the target calendar date (7 days before or 7 days after, inclusive). However, every effort will be made to adhere to this schedule. If critical data (that which would have contributed to primary or secondary endpoints) for a given subject is missed at a timepoint, we will evaluate whether or not data from other time points will be sufficient to conduct the study analyses adequately. If the data is not sufficient to analyze specified endpoints, the subject's data may be excluded entirely or partially, depending on the specific endpoints in question, and in consultation with the biostatistician.

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APPENDIX A. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self- care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self- care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B. CURRENT NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

Please use the following link to the NCI CTCAE website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm