THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

Phase II, single arm, open label single-center study of Obinutuzumab and Ibrutinib in the front line treatment of Indolent Non-Hodgkin's Lymphomas

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IND/IDE Holder:	Thomas Jefferson University
IND/IDE Number:	134835
Study Product:	Ibrutinib Obinutuzumab
Protocol IDs:	JeffTrial # 10049 PRC # 2017-035 IRB Control # 17P.176

Version Number:	Version Date:
1	02/10/2017
1.1	03/27/2017
1.2	4/20/2017
2.0	05/03/2017
2.0.1	05/03/2017
3.0	04/30/2018
3.1	09/06/2018
4.0	11/21/2018
5.1	05/17/2019
6.0	11/21/2019
7.0	06/24/2021
7.1	01/06/2022
7.2	03/14/2022
8.0	03/29/2022
9.0	12/21/2022
10.0	03/14/2023
11.0	08/22/2023
12.0	04/18/2024
13.0	03/26/2026

without prior written authorization from the study sponsor.

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Signature Page

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Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Thomas Jefferson University research policies

List of Abbreviations

ABC	Activated B cell
ADCC	Antibody dependent cellular toxicity
AE	Adverse Effect
BCR	B cell receptor
aNHL	Aggressive non-hodgkin's lymphoma
BR	Bendamustine and Rituximab
BTK	Bruton tyrosine kinase
CD	Cluster differentiation
Clb	Chlorambucil
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CRF	Case report form
CR/CRu	Complete response/ complete response unconfirmed
CTCAE	Common terminology criteria for adverse events
CVAD	Cyclophosphamide, Vincristine, Adriamycin, Dexamethasone
DLBCL	Diffuse large B cell lymphoma
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Co-operative Oncology Group
FDA	Food and Drug Administration
FL	Follicular Lymphoma
FCBP	Females of Child Bearing Potential
FCM	Fludarabine, Cyclophosphamide, Mitoxantrone
FR	Fludarabine, Rituximab
GCB	Germinal center B-cell like
GELF	Groupe d'Etude des Lymphomes Folliculaires
GLSG	German low grade Lymphoma Study Group
G+Clb	Obinutuzumab and Chlorambucil
HR	Hazard Ratio
iNHL	Indolent non-hodgkin's lymphoma
IRB	Institutional review board
IRR	Infusion related reaction

KCC	Kimmel Cancer Center
LDH	Lactose dehydrogenase
MRD	Minimal residual disease
MCL	Mantle cell lymphoma
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin's lymphoma
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PR	Partial response
PET	Positron emission tomography
PD	Progressive disease
PI	Principal Investigator
RIO	Revlimid, Ibrutinib, Obinutuzumab
R-CHOP	Rituximab, Cyclophosphamide, hydroxydoxorubicin, Oncovin,Prednisone
RCVP	Rituximab, Cyclophosphamide, Vincristine, Prednisolone
RFM	Rituximab, Fludarabine, Mitoxantrone
SLL	Small lymphocytic lymphoma
SD	Stable disease
TNF	Tumor necrosis factor
TJU	Thomas Jefferson University
WHO	World Health Organization
XLA	X-linked agammaglobulinemia
XID	X linked immunodeficiency

Study Summary

Title: Phase II, single arm, open label multi-center study of Obinutuzumab and Ibrutinib in the front line treatment of Indolent Lymphomas

Précis: This is a phase II trial evaluating the efficacy of the combination of ibrutinib and obinutuzumab in treatment naïve patients with indolent lymphomas. Patients who are previously untreated will enter the induction phase for up to 6 cycles of IV obinutuzumab and PO ibrutinib. Patients who are in at least stable disease (SD, PR, or CR) will continue obinutuzumab maintenance therapy every 2 months for 2 years. Biopsies, blood draws, and imaging will be performed accordingly.

Objectives: Primary Objective:

To assess efficacy of the combination of ibrutinib and obinutuzumab in chemotherapy naive patients with indolent lymphomas.

Secondary Objective:

- To assess safety and tolerability of the combination.
- To assess Progression free survival rates and Overall survival rates in indolent lymphomas.
- To evaluate response using PET and correlate PET negativity with durability of response.

Population: This study will enroll adult males/females, diagnosed with previously untreated stage II-IV indolent non-hodgkin's lymphomas.

Phase: Phase II

Number of Sites: 1 site: Thomas Jefferson Health System, Center City, Pennsylvania

Description of Intervention: This is a single arm, open-label study involving the 2 drugs – Ibrutinib and Obinutuzumab.

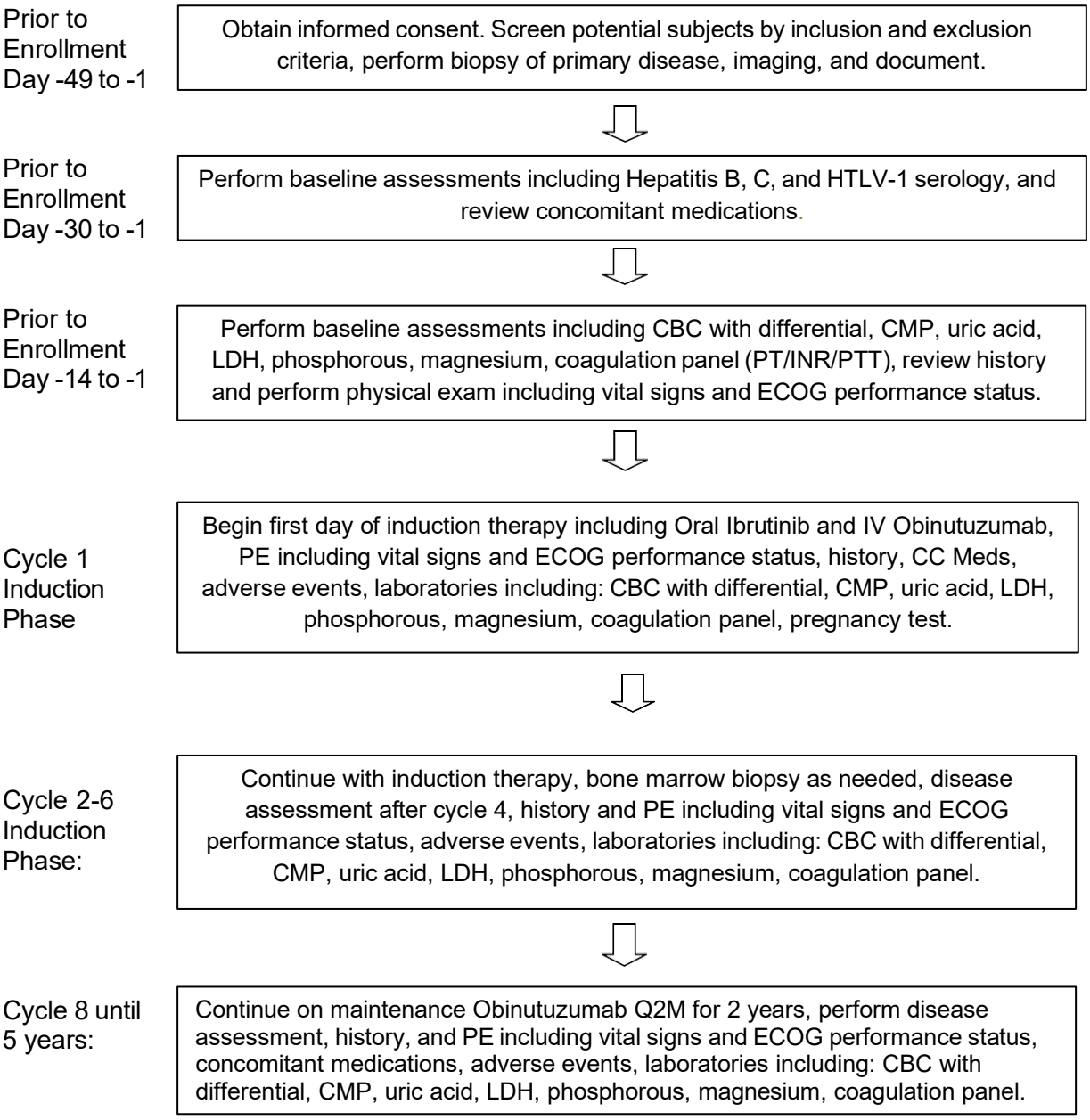
- Ibrutinib: 560 mg orally once daily on days 1-28 until disease

progression.

- Obinutuzumab
  - **Induction**: Obinutuzumab administered by IV infusion for up to 6 cycles (28-day cycles):
    - On Cycle 1, Days 1, 8, and 15, 1000 mg of obinutuzumab will be administered.
    - On Cycles 2 – 6, Day 1, 1000 mg of obinutuzumab will be administered
  - **Maintenance**: Patients who achieve at least a partial response after cycle 7 will continue to receive maintenance therapy as follows: 1000 mg of obinutuzumab will be administered to start 2 months after cycle 6 and will be given every 2 months for a total of 12 doses.

Study Duration:	14 Years (168 months)
Participant Participation Duration:	Patients that achieve PR, will receive obinutuzumab infusions for 24 months in maintenance. Ibrutinib may be continued indefinitely. Total duration of therapy for each patient is until disease progression or until undesired toxicity. Duration of follow up: Patients will be followed for up to 5 years from the date of enrollment.
Estimated Time to Complete Enrollment:	7 years (84 months)

Schematic of Study Design:



1 Introduction

1.1 Background Information

Natural history of indolent lymphomas

For clinical purposes, non-Hodgkin's lymphomas (NHL) can be grouped into indolent and aggressive lymphomas. Both follicular and marginal zone lymphoma are considered indolent B cell lymphomas. These diseases remain a challenge to treat for a number of reasons: they are incurable diseases, they tend to require multiple treatments and patients often have long survival times. Treatment is usually based on symptoms and tumor burden.

Treatment for indolent b-cell lymphomas

Traditional treatment options for indolent b-cell lymphomas included observation for patients who are asymptomatic and multi-agent chemo-immunotherapy for patients who are symptomatic, have a high tumor burden, or other indication for treatment. Biologic therapy has become an integral part of therapy and includes agents that specifically target B-lymphocytes such as monoclonal anti-CD20 antibodies. Although the initial response to these biologic and cytotoxic therapies can be high, nearly all patients relapse. With each subsequent line of therapy, response rates decrease and become less durable but the cumulative toxicities increase. Novel therapeutic options that have shown significant activity have recently arisen from agents that target molecular or B-cell signaling pathways. Combinations of these novel agents with biologic therapy will provide the opportunity to explore a non-chemotherapy approach as front-line therapy in patients in need of treatment and to improve outcomes in patients with indolent b-cell lymphomas.

Chemo-immunotherapy with the addition to rituximab to various chemotherapy combinations (cyclophosphamide, vincristine, prednisone (CVP), cyclophosphamide, adriamycin, vincristine, prednisone (CHOP), bendamustine (B), fludarabine based regimens (F)) has been found to be superior to chemotherapy alone.

No particular regimen has been shown to be superior to the rest. This was demonstrated in the FOLL-05 trial which compared RCVP, R-CHOP and RFM as first line therapy in advanced FL. No significant differences were observed between treatment arms for ORR or CR rates. Grade 3 or 4 neutropenia was more common in the R-FM arm, occurring in 64% of patients, compared with 28% with R-CVP and 50% with R-CHOP. The incidence of secondary malignancies was also more common with R-FM (8%) than with R-CVP (2%) or R-CHOP (3%).[1]

Bendamustine has been shown to be a potent, selective, cytotoxic agent against B lymphocytes with synergism between bendamustine and rituximab observed in both CD20+ lymphoma cell lines and on ex vivo cells from patients with B-CLL or B-cell lymphomas. The pivotal, multicenter, randomized Phase 3 study, conducted by the StiL, enrolled 549 patients with advanced indolent NHL or MCL to treatment with either bendamustine in combination with rituximab (BR) or standard R-CHOP in the first-line setting. Among all patients, response was similar between the two patient groups with an ORR for BR of 92.7% for BR and 91.3% for R-CHOP; however, CR rate was improved for BR (40%) compared with R-CHOP (31%). BR was associated with a superior PFS compared with R-CHOP (BR: 54.9 vs CHOP-R: 34.8 months (median), HR = 0.57 (95% CI: 0.43 - 0.76; p = 0.00012) as was the time to next treatment (BR: not reached vs CHOP-R: 37.5 months (median), R = 0.52 (95% CI: 0.38 - 0.70), p = 0.00002). No differences in OS were noted. BR also showed a better tolerability profile.[2] The BRIGHT study (phase III) compared 6 cycles of BR to 6-8 cycles of R-CHOP in patients with previously untreated indolent NHL (83%) or mantle cell Lymphoma (17%). Among 419 evaluable patients, the CR rate with BR was not inferior to R-CHOP/R-CVP (31% vs. 25%). Adverse effects had similar frequency but were different with less neutropenia but more infusion reactions in the BR group.[3]

Role of Bruton Tyrosine Kinase in low grade b-cell lymphomas

The B cell receptor (BCR) consists of surface immunoglobulin non-covalently bound to the heterodimer CD79a/CD79b. In normal B cells, ligation of the BCR results in a signaling cascade that can lead to proliferation, apoptosis, or anergy depending on the stage of development and antigen ligated.[4] In leukemic b-cells cells, however, the BCR is dysregulated and activation through antigen ligation or auto-stimulation results in the propagation of proliferative and pro-survival signals.[5] Thus, the BCR represents a therapeutic target in indolent b-cell lymphomas. There are currently two agents clinically available that target different aspects of the BCR in phase III studies: Idelalisib (formerly CAL- 101), which is an inhibitor of PI3-kinase p110 delta, and ibrutinib, which inhibits Bruton's Tyrosine Kinase. BTK is a member of the Tec family of kinases, and is an integral kinase involved in B cell signaling and B lymphocyte development and differentiation. Mutation of the gene encoding BTK, located at Xq21.33-q22 is responsible for X-linked agammaglobulinemia (XLA),[6, 7] a disorder characterized by developmental arrest at the pre-B stage and profound humoral immune deficiency in humans, and the milder X-linked immunodeficiency (XID) phenotype in the mouse.[8] BTK is a crucial mediator of BCR signaling in normal and abnormal B cells. Activation of BTK results in cell survival and proliferation through the MAP kinase pathway, PI3K/Akt pathway, and NF-κB. Because of the key role of BTK in B-cell signaling, this is an attractive drug target.

1.1.1 Ibrutinib Background

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways. Ibrutinib is an orally administered, specific, irreversible, and highly potent BTK inhibitor. It binds covalently to a cysteine-481 residue at the active site of BTK, resulting in potent inhibition of kinase activity, with an IC50 of 0.5 nM for more than 24 hours.[9] Pharmacologic inhibition of BTK with ibrutinib has been shown to cause modest apoptosis in vitro, and significantly inhibits B cell proliferation and signaling both in vitro and in vivo.[10]

Ibrutinib has been approved in many regions, including the US and EU, for indications covering the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL) including CLL with a deletion of the short arm of chromosome 17 (del17p) or a TP53 mutation, and patients with Waldenström's macroglobulinemia. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

Tolerability and Efficacy of Ibrutinib Monotherapy

Fowler et al presented results of a Phase 1 dose escalation study which consisted of 16 relapsed / refractory evaluable follicular patients dosed with ibrutinib as monotherapy. Patients were heavily pretreated with a median of 3 prior therapies, and 44% had high risk Follicular Lymphoma International Prognostic Index scores. The ORR in 16 subjects was 44% with 3 CRs and 4 PRs. For those patients with at least 1 tumor response assessment, the median PFS in dose cohorts greater or equal 2.5 mg/kg (n=11) was reported at 13.4 months with an ORR=55%. With patients treated at greater or equal 5 mg/kg (n=9) the median PFS was reported as 19.6 months with an ORR=56%. The drug was well tolerated with no apparent cumulative toxicity upon extended dosing in this study.[11]

Another phase I trial evaluated ibrutinib in 56 patients with a variety relapsed or refractory B-cell lymphoma or CLL. Fifty-six patients with were treated over seven cohorts. Most adverse events were grade 1 and 2 in severity and self-limited. Dose-limiting events were not observed, even with prolonged dosing. The MTD was not reached in this trial at a dose of 12.5 mg/kg. Objective response rate in 50 evaluable patients was 60%, including complete response of 16%. Median progression-free survival in all patients was 13.6 months.[12]

Tolerability and Efficacy of Ibrutinib Combination Therapy

With its single agent activity in NHL, several trials investigated combining ibrutinib with other agents. Ibrutinib has been studied in combination with rituximab in R/R CLL (n = 40) in a phase 2 single-center study of 40 high-risk patients with CLL.[13] Patients were treated with ibrutinib 420 mg daily and weekly rituximab (375 mg/m2) for weeks 1–4 (cycle 1), then daily ibrutinib plus monthly rituximab until cycle 6. This was then followed by ibrutinib daily. The median age was 65 (range 35–82) with a median of 2 prior therapies. Among these, 19 patients had del17p or TP53 mutation (4 without prior therapy), 13 patients had del11q. At a median follow-up of four months, 20 patients were evaluable for response. The overall response rate was 85%, with three cases of partial remission and persistent lymphocytosis. The treatment was well tolerated, with mostly grade 1 to 2 adverse events, and only 13 cases of grade 3 or 4 toxicity, including neutropenia, fatigue, pneumonia, and bone pain.

Ibrutinib was combined with bendamustine (B) and rituximab (R) in a phase I study in patients with relapsed/refractory NHL (FL, MZL, MCL, transformed NHL, and DLBCL). Treatment consisted of standard rituximab and bendamustine doses, with escalating doses of ibrutinib (280 mg or 560 mg) every 28 days for 6 cycles. Ibrutinib was continued after cycle 6 in responding patients. Patients were heavily pretreated with a median of 3 prior therapies (range 0–10). The overall response (OR) rate was 72%, with 52% complete responses). By histology, the OR rate was 90% (50% CR) in FL. Grade 3 to 4 toxicities included lymphopenia (77%), neutropenia (33%), thrombocytopenia (19%), and rash (25%).Median progression-free survival was not reached (95%CI, 8.7 months to not reached)The recommended phase 2 dose of

Ibrutinib in combination with R-bendamustine in patients with NHL was determined at 560mg.[14] A phase III trial in patients with relapsed/refractory indolent NHL with a combination of ibrutinib with R-CHOP or R-bendamustine has completed accrual and results are anticipated soon (NCT01974440).

Given its efficacy and relative safety, ibrutinib was investigated in first line management in patients with follicular lymphoma. A phase 2 multicenter trial investigated the combination rituximab and ibrutinib in patients with newly diagnosed follicular lymphoma (Grade 1, 2 and 3a, stage II-IV disease). Patients with treatment-naïve, histologically confirmed follicular lymphoma received oral ibrutinib 560 mg once daily until progressive disease (PD) or unacceptable toxicity, combined with rituximab. At baseline, 80% of patients had Stage III/IV disease, and 10% of patients had grade 3a FL. At a median follow-up of 10.2 months (range, 1.2–16.2), the investigator-assessed ORR was 82% (95% CI: 70.1–89.4), with a CR rate of 27% and PR rate of 55% in all treated patients. Grade ≥3 AEs occurred in 43% of patients, and those occurring in >1 patient included fatigue and maculopapular rash (5% each), and neutropenia and hypertension (3% each). Overall, the study treatment was well tolerated.[15]

1.1.2 Obinutuzumab

Anti-CD20 monoclonal antibodies have formed the backbone of therapy in most B-cell malignancies. Up until a few years ago, Rituximab in combination with chemotherapy was the standard of care in the treatment of indolent b-cell lymphomas. Obinutuzumab (GA101, RO5072759), is a glycoengineered third generation, humanized, type II anti-CD20 monoclonal antibody). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics: high antibody- dependent cellular cytotoxicity (ADCC); high affinity binding to the CD20 antigen; low complement-dependent cytotoxicity (CDC) activity; and antibody dependent cellular phagocytosis (ADCP) through recruitment of Fc RIII positive immune effector cells such as natural killer (NK) cells, macrophages and monocytes; and high direct cell death induction.

Obinituzumab differs from rituximab since it does not activate complement dependent toxicity and is superior to rituximab in terms of ADCC and direct B-cell killing.[16] Type I and II monoclonal antibodies differ in their CD20 binding and activation of cell death pathways.[17] Type I antibodies (rituximab) induce migration and stabilization of CD20-mAb complexes into lipid rafts and activate CDC. Type II antibodies (obinutuzumab) do not induce this translocation or activate CDC. They stimulate direct cell death associated with actin reorganization and homotypic adhesion, distinct from classical apoptosis.[18, 19] Obinutuzumab has superior killing activity vs rituximab in nonmalignant and CLL cells in in-vitro and ex vivo whole-blood assays 5,8,9 and xenograft models.[20]

1.2 Rationale for the Proposed Study

Obinutuzumab is an anti CD20 monoclonal antibody, which has several mechanisms of action of which antibody dependent cellular cytotoxicity (ADCCC) is predominant. Recent data suggests higher CR rate with obinutuzumab compared to rituximab in patients with relapsed indolent lymphomas [21]. Ibrutinib is another agent that is effective in newly diagnosed follicular lymphoma [15] and other indolent lymphomas [12]. The combination of obinutuzumab and ibrutinib is an attractive ‘chemotherapy free’ combination for patients with indolent lymphomas.

1.3 Correlative Studies

Clinical Experience with Obinutuzumab in Non-Hodgkin Lymphoma

As of 02 July 2015, obinutuzumab has been administered to 2105 patients with NHL in 4 monotherapy studies and 6 combination therapy studies. The combination therapy studies include the following:

- Study BO21000 (GAUDI): A Phase Ib, open-label study of obinutuzumab in combination with CHOP, fludarabine/cyclophosphamide (FC), or bendamustine in

patients with CD20□ B-cell FL. A total of 137 patients were enrolled, including 56 with R/R disease (obinutuzumab □ FC: n □ 28; obinutuzumab □ CHOP: n □ 28) and 80 first-line patients (obinutuzumab □ bendamustine: n □ 41; obinutuzumab □ CHOP: n □ 40).

- Study GAO4915g (GATHER): A Phase II, open-label study of obinutuzumab □ CHOP in previously untreated advanced DLBCL. A total of 100 patients were enrolled.
- Study GAO4753g (GADOLIN): A Phase III study of obinutuzumab □ bendamustine (G- benda) vs. bendamustine alone in patients with rituximab-refractory CD20□ indolent NHL (iNHL). A total of 194 patients were randomized to the G-benda arm and 202 to bendamustine arm.
- Study BO21223 (GALLIUM): A Phase III study of G-chemo vs. R-chemo in patients with advanced iNHL. Enrollment to the study has completed with 1401 enrolled patients; the study is ongoing.
- Study BO21005 (GOYA): A Phase III study of G-CHOP vs. R-CHOP in patients with previously untreated CD20□ DLBCL. Enrollment to the study has completed with 1418 enrolled patients; the study is ongoing.
- Study JO29737 (GATS): A Phase II, open-label study of obinutuzumab (shorter duration of infusion) in patients with CD20□ NHL. Enrollment is ongoing, with 14 patients enrolled (planned enrollment of 36).

Clinical Efficacy in Non-Hodgkin's Lymphoma

In the monotherapy setting (studies BO20999, BO21003, YP25623, and JO21900), the proportion of patients who had a response (CR or PR) at the end of treatment ranged from 28% (11/40 patients) to 58% (7/12 patients). Although patients had treatment-refractory (including rituximab-refractory) or relapsed disease, some patients in studies BO20999, BO21003 (Phase II), and JO21900 achieved a CR by the end of treatment assessment.

In the chemotherapy combination studies BO21000 and GAO4915g, the proportion of patients achieving a response exceeded 90% among FL patients and was 82% among DLBCL patients. The CR rate was also higher (35%□50% of patients with FL and 55% of patients with DLBCL) than in the monotherapy studies.

Data from the pivotal chemotherapy combination Phase III study (GAO4753g) in patients with FL showed that treatment with G-benda for 6 cycles (28 days per cycle) followed by 2-year monotherapy with obinutuzumab resulted in a clinically meaningful and

statistically significant increase in PFS compared with bendamustine alone. The primary objective of the study was to evaluate PFS as determined by an Independent Review Committee (IRC). Median observation time was 21.1 months. The median IRC-assessed PFS in the bendamustine arm was 13.8 months. Median IRC-assessed PFS was not reached in the G-benda arm (PFS hazard ratio [HR] □ 0.48, 95% CI: 0.34□0.68; stratified log-rank test p-value □ 0.0001). The investigator- assessed PFS result was consistent with the IRC-assessed PFS. The median investigator- assessed PFS in the bendamustine arm was 13.7 months, and the median in the G-benda arm was 29.2 months (PFS HR □ 0.48, 95% CI: 0.35□0.67; stratified log-rank test p-value □ 0.0001). IRC-assessed best ORR within 12 months from the start of treatment was 78.7% in the G- benda arm (15.5% CR and 63.2% PR) and 74.7% (18.7% CR and 56.0% PR) in the bendamustine arm. An analysis conducted with 24.1 months of median observation time revealed that the median OS was not yet reached in either arm.

Overview of Safety

Integrated safety data from a total of 422 subjects with B-cell malignancies from 4 combination therapy studies that have completed primary analysis or final analysis included in the CSR as of 31 July 2017 are briefly summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Table 1: Most frequently reported Treatment-Emergent Adverse Events (TEAEs) in subjects receiving ibrutinib in combination therapy (N=422):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >5%	Most frequently reported Serious TEAEs >2%
Neutropenia	Neutropenia	Neutropenia
Diarrhea	Diarrhea	Diarrhea
	Nausea	
	Thrombocytopenia	
Nausea	Fatigue	Thrombocytopenia
	Anemia	
Thrombocytopenia	Pyrexia	Fatigue
Fatigue	Upper respiratory tract infection	Anemia
Anemia	Constipation	Pyrexia
Pyrexia	Vomiting	Pneumonia
Infusion related reaction	Rash	Febrile neutropenia
Upper respiratory tract infection	Headache	Atrial fibrillation
	Pneumonia	Cellulitis

Constipation	Decreased appetite	Hypertension
Vomiting	Contusion	Hyperuricemia
Rash	Febrile neutropenia	Leukopenia
Headache		Neutrophil count decreased
Cough		Tumor lysis syndrome
Muscle spasm		Urinary tract infection
Pneumonia		White blood cell count decreased
Oedema peripheral		
Arthralgia		
Decreased appetite		
Contusion		
Insomnia		
Chills		
Peripheral sensory neuropathy		
Stomatitis		
Febrile neutropenia		
Abdominal pain		
Back pain		
Bronchitis		

Summary of Pharmacokinectics

Following oral administration of ibrutinib at doses ranging of 420, 560, and 840 mg/day, exposure to ibrutinib increased proportionally with substantial intersubject variability. The mean terminal plasma elimination half life (t1/2) of ibrutinib ranged from 4 to 6 hours, with a median time to maximum plasma concentration (Tmax) of 1 to 2 hours. Despite the doubling in mean systemic exposure when dosed with food, the favorable safety profile of ibrutinib allows dosing with or without food. Ibrutinib is extensively metabolized primarily by CYP 3A4 mediated metabolic pathways. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure implying non-clinically relevant accumulation. About 8% of ibrutinib is excreted in the urine. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

1.4 Overview of Safety of Obinutuzumab:

As of 2 July 2015 (the safety data cutoff date for all studies except MO28543), obinutuzumab has been administered to a total of 3386 patients, including 1281 patients with CLL and 2105 patients with NHL, from doses of 50 mg to 2000 mg in monotherapy or in combination with CHOP, FC, bendamustine, or chlorambucil (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 of infectious diseases. This is consistent with the study population and the disease being treated.

Of particular interest, IRRs were observed consistently in all obinutuzumab trials. In patients with CLL (study BO21004), 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, CHOP, or bendamustine) appears similar to that observed with monotherapy. Furthermore, the incidence of IRR appears to be higher with CLL compared with NHL, and higher in patients who received obinutuzumab compared with patients who received rituximab 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, investigating G-Clb vs. R-Clb in patients with CLL, the incidence of IRR, Grade 3□4 IRR, and IRR leading to discontinuation was higher in G-Clb arm compared with the R-Clb arm. This study implemented several measures to minimize the risk of IRRs, including: use of corticosteroids, withdrawal of antihypertensive treatments, slow infusion, and split dosing. 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 IRRs was limited. In the pivotal study GAO4753g in patients with R/R iNHL, the majority of IRRs were Grade 1 or 2 and there were no fatal (Grade 5) IRRs. The overall incidence of IRRs was higher in the G-benda arm compared with the bendamustine arm (69% vs. 63%), as was the incidence of Grade 3□4 IRRs (11% vs. 6%), serious IRRs, IRRs leading to withdrawal from treatment, dose reductions, or dose interruptions.

In Study GAO4753g, the most common adverse reactions (incidence □ 10%) observed in patients with iNHL in the G-benda arm were IRRs, neutropenia, nausea, fatigue, cough, diarrhea, constipation, pyrexia, thrombocytopenia, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis, anemia, asthenia, and urinary tract infection. The most common Grade 3□4 adverse reactions (incidence □ 10%) observed in patients with iNHL in the G-benda arm were neutropenia, thrombocytopenia, and IRRs.

Due to the pharmacological class of obinutuzumab, as well as the evidence from monotherapy Phase I trials and chemotherapy combination trials GAO4779g (Phase I) and BO21004 (Phase III), the Sponsor considers acute thrombocytopenia and thrombocytopenia to be related to obinutuzumab. The main risk associated with thrombocytopenia is hemorrhage. In study BO21004, the overall incidence of hemorrhagic adverse events was comparable between the treatment arms (8.0% G-Clb; 7.2% R-Clb), with the majority of events being of Grade 1 or 2 severity. However, and importantly, all fatal hemorrhagic events in the G-Clb arm occurred in Cycle 1 in contrast to such events in the R-Clb arm, which occurred later (beyond 1 year after first administration of study drug). In the pivotal study GAO4753g in patients with R/R iNHL, the overall incidence of hemorrhagic events was 11% in the G-benda arm and 10% in the bendamustine arm. No fatal hemorrhagic events occurred in the study. Grade 3□4 hemorrhagic events were similar in both treatment arms (5% in the G-benda arm and 3% in the bendamustine arm).

Adverse events of special interest include IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including late-onset and prolonged neutropenia), prolonged B- cell depletion, infections including progressive multifocal leukoencephalopathy (PML) and hepatitis B virus (HBV) reactivation, worsening of pre-existing cardiac conditions, gastrointestinal (GI) perforation, and second malignancies.

Summary of Pharmacokinectic and Pharmacodynamic Data for Obinutuzumab

The clinical pharmacology properties of obinutuzumab have been characterized in a number of clinical studies in patients with CLL or NHL. These studies include two Phase I/II monotherapy studies (BO20999 and BO21003); two Phase I monotherapy studies in Japanese patients with NHL (JO21900) and Chinese patients with FL, DLBCL, or CLL (YP25623); two Phase Ib combination studies (BO21000 and GAO4779g); two Phase II studies (a combination Study GAO4915g and a monotherapy Study GAO4768g at 1000 mg and 2000 mg); and two Phase III combination studies (BO21004/CLL11 and GAO4753g). A serum sampling scheme for the quantitation of obinutuzumab was undertaken in these studies to enable population PK analysis, which 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 was2 □ 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 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, it binds obinutuzumab. With repeated dosing of obinutuzumab, the pool of CD20-positive cells is saturated, thereby reducing this component in clearance. The linear clearance pathway is consistent with catabolism of IgG antibodies and is therefore independent of CD20-positive cells. 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.

Consistent with the mechanism of action of obinutuzumab, extensive B-cell depletion was observed both in patients with NHL and CLL. In most patients receiving obinutuzumab monotherapy, there was no notable increase in complement levels during or following an infusion. Changes in the levels of interleukin (IL)-6 and IL-8 were observed, i.e., increases during the course of the first infusion followed by a decrease to pre-infusion levels 7 days later.

1.5 Potential Risks and Benefits

1.5.1 Potential Risks

1.5.1.1 *Ibrutinib*

Likely (>20%)

Increase in frequency of loose or watery stools (Diarrhea), muscle and joint pain, fever (pyrexia), rash, nausea, low white blood cell count (Neutropenia), bleeding (hemorrhage)

Possible (>10%)

Sores in the mouth, low platelet count (cells that help blood to clot), constipation, swelling of the hands or feet, joint aches, common cold, vomiting, skin infection, pneumonia, headache, muscle spasms, high blood pressure, weakness, tingling, numbness, and pain from nerve damage, usually in the hands and feet (peripheral neuropathy).

Rare (>1%)

Blurry vision, increased level of uric acid in the blood, abnormal heart rhythm (Atrial fibrillation), increase in white blood cell counts, low white blood cell counts with fever, severe infection throughout the body, dizziness, urinary tract infection, non-melanoma skin cancer, breaking of nails (onychoclasis), inflammation within the lungs that may lead to permanent damage (interstitial lung disease), sinus infection.

Very rare (<1%)

Tumor lysis syndrome, itchy rash (urticarial), inflammation of the fatty tissue underneath the skin (panniculitis), angioedema, increase in white blood cell count (lymphocytosis), leukocytosis syndrome, Stevens-Johnson syndrome, liver failure, ventricular tachyarrhythmia.

Bleeding-related Events:

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis and petechiae and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematouria. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced plately aggregation were observed, refer to section Antiplatelet agents and anticoagulants (5.7.5)

Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet functions may increase the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs and symptoms of bleeding.

Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 5.7.5 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See section 5.7.8 for guidance on ibrutinib management with surgeries or procedures.

Cardiac Arrhythmias

Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia including some fatal events have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg., palpitation, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see section 5.4).

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Monitor complete blood counts monthly.

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheal and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as Clostridium difficile or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (section 5.4).

Infections:

Infections (including sepsis, bacterial, viral or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although casuality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see section 5.4).

Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in study 1112. Most rashes were mild to moderate in serverity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson Syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition hypersensitivity-related events including erythema, urticarial, and angioedema have been reported.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions. Refer to section 5.10 for prophylaxis for TLS. Refer to section 5.10 for treatment of TLS.

Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate antihypertensive treatment as appropriate.

Long-term safety:

The long-term safety data over 4 years from 1177 subjects (CLL/SLL n=807 and MCL n=370) treated with ibrutinib were analyzed. The median duration of treatment for CLL/SLL was 45 months with 70% and 40% of subjects receiving treatment for more than 2 years and 4 years. The median duration of treatment for MCL was 11 months with 31% and 14% of subjects receiving treatment for more than 2 years and 4 years. The overall known safety profile of ibrutinib-exposed subjects remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), and 8% (year 3-4). The incidence for the 4-year period was 10%.

1.5.1.2 ***Obinutuzumab***

Hepatitis B Virus 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 such as obinutuzumab. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death. Please refer to section 5.2.3.4 regarding management of hepatitis B.

Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, was observed in patients treated with obinutuzumab. Consider the diagnosis of PML in any patient presenting with new onset or changes to pre-existing neurologic manifestations. Evaluation of PML includes, but is not limited to consultation with a neurologist, brain MRI and lumbar puncture. Discontinue obinutuzumab therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Infusion Related Reactions

Obinutuzumab can cause severe and life-threatening infusion reactions. Sixty-five percent of patients with CLL experienced a reaction to the first 1000 mg infused of obinutuzumab. Thirty-eight percent of iNHL patients experienced a reaction on Day 1 of obinutuzumab infusion. Infusion reactions can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (eg., bronchospasm, larynx, and throat irritation, wheezing, laryngeal edema). Most frequently reported symptoms include nausea, fatigue, dizziness, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Please refer to section 5.9.1 for pre-medications/prophylaxis and section 5.9.2 for management of infusion related reactions.

Tumor Lysis Syndrome

Tumor Lysis Syndrome (TLS) including fatal cases, has been reported in patients receiving obinutuzumab. Refer to section 5.10 for prophylaxis against TLS and sections 5.10 for management of TLS.

Infections

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. Fatal infections have been reported with obinutuzumab. Do not administer obinutuzumab to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection.

Neutropenia

Severe and life threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab. Patients with Grade 3 to 4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection.

Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days).

Refer to section 5.10 for management of neutropenia.

Acute Thrombocytopenia

Acute thrombocytopenia (i.e., thrombocytopenia occurring immediately after infusion) has been rarely observed with rituximab, another anti-CD20 antibody. Possible risk factors for acute thrombocytopenia among subjects exposed to rituximab may be high tumor burden, bone marrow involvement, splenomegaly, and histological subtypes of mantle cell lymphoma and hairy cell leukemia. The mechanism for acute thrombocytopenia development is currently unclear; however, it may be mediated through activation of complement and activation of cytokine cascade during the first administration. Due to the pharmacological class of obinutuzumab, as well as the evidence from monotherapy Phase I studies and studies BO21004 and GAO4779g, the Sponsor considers acute thrombocytopenia to be related to obinutuzumab hemorrhage.

The main risk associated with thrombocytopenia is hemorrhage. In study BO21004, the overall incidence of hemorrhagic AEs was comparable between the treatment arms (7.8% RCIb vs 8.0% GCIb) with the majority of events being of Grade 1 or 2 in severity. Notably, all fatal hemorrhagic events (4 cases) in the GCIb arm occurred in Cycle 1 in contrast to such events in the RCIb arm (3 cases) which occurred later (beyond 1 year after the first administration of the study drug). In trial BO21000, three patients from the low dose group and 10 patients from the high dose group of G-CHOP arm had hemorrhagic events during the study, these were Grade 1-2 AEs, four AEs were reported in the G 1000mg+ Benda arm; these were Grade 1-3 AEs. The reported terms in the low dose group were mouth hemorrhage, contusion, conjunctival hemorrhage and postmenopausal vaginal bleeding. The reported terms in the high dose group were rectal bleeding, vitreous hemorrhage, gum bleeding, contusion, hematuria, vaginal bleeding, epistaxis. In study GAO4735g (R/R iNHL population although the incidence of hemorrhagic AEs in G-benda arm was higher (11.8%) than in the BO21004 study (GCIb:8.0%), it was similar with the comparator arm, benda (11.2%). More serious events were reported in G-Benda arm (2.9% vs 1.5%), but no fatal hemorrhagic events were reported.

Gastrointestinal Perforation

The most common causes of GI perforation in cancer patients are spontaneous perforation secondary to tumor (either primary or metastatic), iatrogenic perforation secondary to instrumentation (endoscopy) or cancer treatment. Perforation secondary to tumor is mainly relevant in NHL patients, as GI tract involvement is much more frequent in this patient population than in CLL patients. If the wall of the GI tract is significantly infiltrated by tumor cells, tumor necrosis as a spontaneous occurrence or upon radiation or antilymphoma therapy may lead to bowel perforation. Even in the absenece of involvement of the wall of

the GI tract by tumor, severe gastroenteritis due to radiation or chemotherapy may lead to severe bowel dilatation or distension and subsequent perforation. Bowel perforation can also occur in severe infections like typhlitis and neutropenic enterocolitis. Based on the mechanism of action (rapid tumor lysis) and on the fact that cases of GI perforation were observed in obinutuzumab treated patients (mainly in NHL), it is considered an important identified risk of obinutuzumab. GI perforation may result in peritonitis with a potentially fatal outcome. It generally requires surgical intervention. GI perforation may affect the upper or lower GI tract. Upper bowel perforation can be either free (when bowel contents spill freely into the abdominal cavity, causing diffuse peritonitis e.g. duodenal or gastric perforation) or contained (when a full-thickness defect is created but free spillage is prevented because contiguous organs wall off the area e.g., duodenal ulcer perforation into the pancreas). Lower bowel perforation (e.g., in patients with acute diverticulitis or appendicitis) results in free intraperitoneal contamination and peritonitis.

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.

1.5.2 Benefits

There may be no benefit from being in this research, but we hope that what we learn may be helpful to future patients or society in general.

2 Study Objectives

2.1 Objectives

2.1.1 Primary

To assess the efficacy of the combination of ibrutinib and obinutuzumab in chemotherapy naïve patients with indolent lymphomas.

2.1.2 Secondary

- To assess Progression free survival rates and overall survival rates in indolent lymphomas.
- To assess safety and tolerability of the combination.

- To evaluate response using PET and correlate PET negativity with durability of response.

2.2 Endpoints/Outcome Measures

2.2.1 Primary Endpoint

Overall response rate following 7 cycles of therapy in patients with untreated stage II-IV indolent lymphomas requiring treatment. This constitutes complete response (CR) and Partial response (PR). Response will be assessed by the revised Lugano (See section 6.1.9 and Appendix 9)

2.2.2 Secondary Endpoint

- 1 year, 3 year and 5 year progression free survival
- 1 year, 3 year, and 5 year overall survival
- Incidence of Grade III-IV toxicity
- Compare progression free survival in patients with PET negative disease at the end of the cycle 7 to those with PET positive disease

3 Study Design

3.1 Characteristics

3.1.1.1 *General Design*

This is a phase II study designed to identify the efficacy of the combination of ibrutinib and obinutuzumab in patients with untreated indolent lymphomas (follicular lymphoma and marginal zone lymphoma). Patients with follicular lymphoma and marginal zone lymphoma stage II-IV with an indication for therapy per standard modified GELF criteria including: Symptoms attributable to lymphoma, B symptoms, threatened end-organ function, pleural effusions or peritoneal ascites, cytopenia secondary to lymphoma, bulky disease (defined as single mass >7 cm in diameter, or 3 or more masses >3 cm in diameter), splenomegaly, and steady progression over at least 6 months will be screened.

All enrolled patients will have 7 cycles of induction therapy at the described dose and schedule (Obinutuzumab will not be given in Cycle 7). Following the 7^{th} cycle of therapy, they will continue with ibrutinib at the same dose and schedule until disease progression or intolerable toxicity. Patients that achieve PR will also continue with obinutuzumab maintenance every 2 months for 2 years (total of 12 doses). Patients will be restaged with PET/CT scans after 4 cycles of induction therapy have been completed (scan should be performed approximately halfway through cycle 5). Patients who are in at least stable disease (SD, PR or CR) after 4 cycles will receive 3 subsequent cycles. Patients who achieve at least a partial response after cycle 7 will

then proceed to maintenance therapy. Patients who have progressive disease (PD) or stable disease (SD) after cycle 7 will discontinue protocol treatment. All patients will be followed up for a total of 5 years.

The protocol therapy will be continued until:

1- The patient withdraws consent

2- Disease progression

3- Unacceptable toxicity

4- Suspected pregnancy

The study drug combination consists of:

- **Ibrutinib:** 560mg PO daily on day 1-28 until disease progression or toxicity
- **Obinutuzumab:** Cycle 1: 1000mg IV infusion every week on days 1, 8, and 15.

  Cycle 2-6: 1000mg IV infusion on Day 1 of each cycle.

  Maintenance: Cycle 6 is followed by 1000mg IV infusion every 2 months for 2 years.

3.2 Number of Participants

30+

3.3 Duration of Therapy

Obinutuzumab will be given up to 2.5 years and Ibrutinib until disease progression.

3.4 Duration of Follow Up

Patients will be followed for survival for 5 years from the date of Survival Follow-up clarification enrollment. For patients who remain on study treatment beyond 5 years, the follow-up period will be 30 days from the last dose of study drug.

3.5 Treatment Assignment Procedures

3.5.1 Randomization Procedures (if applicable)

N/A. This is a single arm study.

3.5.2 Masking Procedures (if applicable)

N/A

3.6 Study Timeline

3.6.1 Primary Completion

We anticipate accrual of 30 patients to the study over a 84 month time period. Patients will remain on study for 2 years of Maintenance and will be followed for 5 years.

3.6.2 Study Completion

We anticipate completion of the study in 14 years.

4 Study Enrollment and Withdrawal

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

1. Previously untreated, histologically confirmed indolent non-hodgkin's lymphoma who have not received prior systemic therapy (prior radiation or steroid treatment is allowed) as follows:
    - Follicular lymphoma (WHO classification grade 1, 2, or 3a)
    - Marginal zone lymphoma including:
        - Nodal and splenic MZL who have an indication for systemic therapy
        - Extranodal MZL:
            - Non-gastric/non-cutaneous MZL requiring systemic therapy
            - Cutaneous MZL will be eligible only if they have pathologically confirmed extra-cutaneous disease
            - Gastric MZL only if stage IIIE/IV defined as lymph node involvement on both sides of the diaphragm or with disseminated extranodal disease such as bone marrow or additional extra nodal sites.
2. Pathological diagnosis should be obtained by incisional or excisional tissue biopsy. Core biopsy is permissible if obtaining an incisional or excisional is not possible and if the grade can be assessed on the core biopsy. A core biopsy can also be used if deemed in the best interest of the patient in the opinion of the investigator.

3. Patients must have stage II-IV disease.
4. All patients should have measurable disease. Measurable disease is defined as a lymph node or tumor mass that is ≥1.5cm in at least one dimension by CT or the CT portion of the PET/CT.
5. Documentation of CD20+ status.
6. Patients must have an indication for therapy per standard modified GELF criteria including:
    - Symptoms attributable to lymphoma
    - B symptoms
    - Threatened end-organ function
    - Pleural effusions or peritoneal ascites
    - Cytopenia secondary to lymphoma
    - Leukemia
    - Bulky disease (defined as: Single mass >7cm in diameter, or 3 or more masses >3cm in diameter)
    - Splenomegaly
    - And steady progression over at least 6 months.
7. Age >18 years.
8. ECOG performance status 0-2
9. Patients must be able to swallow whole pills.
10. Ability and willingness to comply with the requirements of the study protocol. When it is determined by the study investigator that a potential research participant is cognitively impaired, a surrogate consent from a caregiver or legally-authorized representative will be obtained. Caregiver or legally-authorized representative will ensure that they comply with the protocol in order for the subject to be considered eligible.
11. Female subjects who are of non-reproductive potential (i.e., post-menopausal by history – no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative urine/serum pregnancy test upon study entry.

12. Male female subjects who agree to use both a highly effective method of birth control (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence, or sterilized partner) and a barrier method (e.g., condoms, vaginal ring, sponge, etc) during the period of therapy. Female patients of reproductive potential who are not surgically sterile must practice adequate birth control for a minimum of twelve months post- treatment; male patients who are not surgically sterile must practice adequate birth control for a minimum of three months post-treatment.

13. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening, with the exception of pegylated GCSF (pegfilgrastim) and darbopoeitin which require at least 14 days prior to screening defined as:

    - Absolute neutrophil count >1.5x10^9 cells/mm^3
    - Platelet count >50000 cells/mm^3 (50x10^9/L)
    - Hemoglobin >9.0 g/dL

14. Adequate hepatic and renal function defined as:

    - Serum aspartate transaminase or alanine transaminase $\leq$3.0 x ULN
    - PT/INR <1.5 x ULN and aPTT <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder)
    - Estimated Creatinine Clearance $\geq$30 ml/min (Calculated according using Cockcroft-Gault formula)
    - Bilirubin $\leq$1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome of non-hepatic origin)

15. Patients with Child Pugh B or C liver failure will be excluded

4.1.2 **Exclusion Criteria**

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Prior history of malignancies unless the patient has been disease free for $\geq$5 years. Exceptions include basal cell carcinoma or squamous cell carcinoma of the skin; carcinoma in situ of cervix; carcinoma in situ of breast, localized prostate cancer, or superficial bladder cancer that has undergone curative therapy.

2. Prior therapy for lymphoma including chemotherapy or immunotherapy including ibrutinib/anti-CD20 agents.
3. Corticosteroid use within 2 weeks prior to study treatment.
4. Known prior significant hypersensitivity to obinutuzumab (not including infusion reactions) or Ibrutinib.
5. Patients with evidence of large B cell transformation (transformed disease are not eligible).
6. Known central nervous system (CNS) involvement by lymphoma
7. Known bleeding disorders (e.g., von Willebrand's disease or hemophilia)
8. Concomitant use of warfarin or other Vitamin K antagonists
9. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (See Appendix 5).
10. Known active bacterial, viral, fungal, mycobacterial, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (related to the completion of the course of antibiotics) within 4 weeks before the start of cycle 1.
11. Known infection with human immunodeficiency virus (HIV) or human T-cell leukemia virus 1 (HTLV-1) seropositive status
12. Viral hepatitis:
    - Patients with active hepatitis B defined by hepatitis B surface antigen positivity or core antibody positivity in the presence of detectable serum hepatitis B - DNA viremia are not eligible for this study
    - Patients with positive hepatitis B core antibody but with negative hepatitis B - DNA maybe considered for participation, but must agree to receive appropriate anti-hepatitis B viral therapy suppression therapy while on obinutuzumab and have hepatitis B DNA monitored every 4 weeks with real time PCR by the treating physician. These patients should be referred to a hepatologist or gastroenterologist for appropriate monitoring and management.
    - Hepatitis C: Patients with positive hepatitis C serology unless HCV RNA is confirmed negative by PCR.
13. Vaccination with a live vaccine a minimum of 28 days prior to the start of treatment

14. Patient is receiving other investigational drugs
15. Prior chemotherapy for any other cancer within the last 2 years
16. Patients should not have active or uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
17. Patients should not have transfusion-dependent thrombocytopenia or bleeding disorders
18. Patients should not have an autoimmune disorder that requires active immunosuppression
19. Patients should not have a history of uncontrolled seizures
20. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment on the study
21. Patients should not have a stroke or intracranial hemorrhage within last 6 months.
22. Prior Surgery: Patients may not have had major surgery within 28 days of enrollment, or minor surgery within 7 days of enrollment. Examples of minor surgery include dental surgery, insertion of a venous access device, skin biopsy, or aspiration of a joint. The decision about whether a surgery is major or minor can be made at the discretion of the treating physician.
23. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
24. Pregnant and nursing: Female patients must have a negative serum pregnancy test within 72 hrs prior to initiating protocol therapy and be practicing an effective form of contraception during protocol therapy and for at least 18 months following completion of protocol therapy.
25. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix 5).

4.2 Gender/Minority/Pediatric Inclusion for Research

This study is only designed for adults and thus all patients below (but not including) the age of 18 years are excluded from this study. There is no limitation on the inclusion of patients with respect to gender and race/ethnicity. However, women who are pregnant or nursing will be excluded due to potential of birth defects which may be caused by the study drug. Men are

overrepresented in non-Hodgkin lymphoma and the male:female ratio is approximately 3:1. The enrollment of women will be monitored quarterly.

4.3 Strategies for Recruitment and Retention

All patients with a diagnosis of untreated follicular lymphoma or marginal zone lymphoma who require treatment are eligible for this clinical study. Subjects will be identified by the referring physician affiliates or referring practices and institutions. There is no upper age limit on this clinical study as long as subjects meet the eligibility criteria. This study will be conducted at the Thomas Jefferson University Hospital.

4.4 Participant Withdrawal

4.4.1 Reasons for Withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study participant's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The most common anticipated reasons for either the treating physician or PI to withdraw patients from this study or the patients asking to be withdrawn are

  (1) Toxicities or intolerance;

  (2) Loss of good faith in the treatment, institution or physician;

  (3) Suspected pregnancy;

  (4) Non-compliance (either due to lack of motivation or due to loss/limitation of a support network). Non-compliance will be defined as following:

  (i) Patient has missed >50% of the doses per cycle of either the ibrutinib as part of the planned therapy without explainable circumstances (weather related, acute illness or hospitalization);

  (ii) Failure to comply with at least 50% of the required lab testing;

  (iii) Uncoorperative with response assessment;

(iv) Missed more than 50% of the required physician follow-up;

(v) suspected pregnancy.

Patients will receive a warning and be notified of the non-compliance withdrawal policy each time they miss the scheduled therapy, lab tests or physician follow-up.

Criteria for Patient Discontinuation

General Criteria

Inability of patient to comply with the study requirements, disease progression including disease transformation, patient's withdrawal of consent at any time, and pregnancy. Also, if the investigator determines that it is no longer safe for the patient to continue therapy.

Obinutuzumab-Specific Criteria

Patients who meet the following criteria should be discontinued from the study:

- Hepatitis B reactivation (hepatitis B viral PCR; >100U/ml) while on hepatitis B antiviral therapy
- Severe or life-threatening anaphylaxis or hypersensitivity reaction

Patients who are carriers of hepatitis B (positive hepatitis B core antibody) at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis.

Ibrutinib-Specific Criteria

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk.

4.4.2 Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention

Patients may withdraw from this study at any time. However, the reason for the withdrawal must be documented by the Principal Investigator (PI) or treating physician.

If the patient withdraws (or is withdrawn) from the study due to non-compliance, they will not be included in the final response analysis but be replaced with another patient.

If however the patient withdraws from the study after documented toxicity, issues with tolerance or ineffectiveness, we will make every effort to obtain efficacy and toxicity data. Such a patient will be included as a treatment failure in the final analysis.

Data Collection and Follow-up for Withdrawn Subjects

Patients who are withdrawn from trial medication will be seen monthly in the outpatient clinic for up to a year. After that, they will be followed every three to six months for 4 years. The final visit will occur 1 year later, at year 5. . We will make good effort to follow up with all patients withdrawn from this study. Patients who are lost to follow up will be defined as the following:

1. Three consecutive “non-shows” for scheduled clinic visits;
2. No reply to at least 2 phone call attempts per month for 3 months

Patients not meeting these criteria are not considered lost to follow-up but are still delinquent in their responsibilities and will be encouraged to follow-up in the form of a scheduled clinic visit or at the very least agree to phone calls in place of scheduled clinic visits.

4.5 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <investigator, funding agency, the Investigational New Drug (IND) /Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

5 Study Intervention

5.1 Study Product

The combination of agents being studied in this clinical trial are ibrutinib and obinutuzumab. Ibrutinib will be administered PO and Obinutuzumab will be administered as an infusion.

5.2 Study Products Description

Ibrutinib capsules are provided as hard gelatin capsules of 140mg each.

Obinutuzumab is provided in single-use vials, each vial containing 41ml (2.5%overfill).

5.2.1 **Acquisition**

Ibrutinib will be provided by Pharmacyclics.

Obinutuzumab will be provided by Genentech.

Both drugs will be stored in the Investigational Drug Services at Thomas Jefferson University.

5.2.2 **Formulation, Packaging, and Labeling**

Ibrutinib

Ibrutinib capsules are provided as hard gelatin capsule containing 140mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib investigators brochure for a list of excipients.

The Ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drugs will be dispensed in child-resistant packaging.

Study drug labels will contain information to meet the applicable regulatory requirements.

Obinutuzumab:

Obinutuzumab is provided by Genentech as a single-use vial, and will be stored at the Investigational Drug Service at Thomas Jefferson University.

Each vial contains a sterile liquid formulation in a 50-ml pharmaceutical-grade glass vial containing a nominal dose of 1000 mg of obinutuzumab (G3 material). The formulated drug product consists of 25mg/ml drug substance formulated in histidine/histindine-HCl, trebalose and poloxamer 188. The vial contains 41ml (with 2.5% overfill).

5.2.3 **Product Storage and Stability**

Ibrutinib:

Ibrutinib will be provided by Pharmacyclics and will be stored in the Investigational Drug Service (IDS) at Thomas Jefferson University. Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drugs will be dispensed in child-resistant packaging. Study drug labels will contain information to meet the applicable regulatory requirements.

Obinutuzumab:

The recommended storage conditions for the obinutuzumab drug product are between 2°C and 8°C, protected from light. Chemical and physical in-use stability for obinutuzumab dilutions in 0.9% sodium chloride (NaCl) at concentrations of 0.2-20 mg/ml have been demonstrated for 24 hours at 2°C-8°C and an additional 24hrs at ambient temperature and ambient room lighting. The prepared diluted product should generally be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C unless reconstitution/dilution has taken place in controlled and validated aspectic conditions. Obinutuzumab should not be frozen or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques. Do not use an additional in line filter because of potential adsorption.

5.3 Dosage, Preparation, and Administration

Ibrutinib:

Ibrutinib dose of 560mg (4x 140mg capsules) is administered orally once daily.

The capsules are to be taken around the same time each day with 8 ounces (approximately 240 ml) of water. The capsule should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

(Refer Section 5.7.6 and Appendix 5 of old protocol)

Obinutuzumab:

Preparation: Obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl.

To prepare a 1000-mg dose: The final drug concentration of 1000-mg dose should be 4 mg/ml. Using a 250-ml infusion bag containing 0.9% NaCl withdraw and discard 40 ml of the NaCl. Withdraw 40 ml of obinutuzumab from a single glass vial and inject into the infusion bag (discard any unused portion of obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution. Do not shake.

Administration: Administration sets with polyvinyl chloride, polyurethane, or polyethylene as product contact surface and IV bags with polyolefin, polypropylene, polyvinyl chloride, or polyethylene as product contact surface are compatible and may be used. Use of a port or peripherally inserted central catheter line is acceptable.

Do not use obinutuzumab beyond the expiration date stamped on the carton.

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be 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 (such as Braun Infusomat Space) should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line should remain in place for at least 2 hours in order to be able to administer IV drugs if necessary. If no AEs occur after 2 hours, the IV line may be removed. For subsequent infusions, the IV line should remain in place for at least 1 hour from the end of infusion, if no AEs occur after 1 hour, the IV line may be removed.

Induction: Obinutuzumab administered by IV infusion for up to 6 cycles (28-day cycles):

- On Cycle 1, Days 1, 8 and 15, 1000mg of obinutuzumab will be administered
- On Cycles 2-6, Day 1, 1000mg of obinutuzumab will be administered.

Maintenance: Patients with at least a partial response after cycle 7 will continue to receive maintenance therapy as follows: 1000mg of obinutuzumab will be administered to start 2 months after cycle 6 and will be given every 2 months for a total of 12 doses (see Table 2).

5.4 Dose Modifications and Dosing Delays

Ibrutinib:

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

Ibrutinib Overdose: There is limited data on the effects of ibrutinib overdose. No maximum tolerated dose (MTD) was reached in the Phase I study in which subjects received up to 12.5mg/kg (1400 mg/day). In a separate study, 1 healthy subject who received a dose of 1680mg experienced reversible Grade 4 hepatic enzyme increases (AST and ALT). Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

5.4.1 Dose Modification for Toxicity

The dose of study drug must be modified according to the dose modification guidelines in Table 2 if any of the following toxicities occur:

- Grade 4 neutropenia (ANC <500/μL) for more than 7 days. See section 5.10 for instructions regarding the use of growth factor support.
- Grade 3 thrombocytopenia (platelets <50,000/μL) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia (platelets <25,000/μL).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic

and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (See Section 5.7.5)

Patients with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period. Antiviral and antifungal prophylaxis should be considered.

If the dose of ibrutinib/placebo is reduced, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the Dose Administration eCRF.

Table 2. Ibrutinib Dose Modifications

Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	- Withhold ibrutinib until recovery to an ANC ≥750 µL or platelets >25,000 µL with no evidence of Grade ≥2 bleeding; may restart at original dose level - Patients with Grade 3 Thrombocytopenia in the presence of Grade 2 bleeding must hold treatment until the Grade 2 bleeding resolves. If grade 2 bleeding resolves in the presence of Grade 3 thrombocytopenia; may restart at original dose level
Subsequent	- Withhold ibrutinib until recovery to an ANC ≥750 µL or platelets >25,000 µL with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower (refer to Table 5) - Patients with Grade 3 Thrombocytopenia in the presence of Grade 2 bleeding must hold treatment until the Grade 2 bleeding resolves If grade 2 bleeding resolves in the presence of Grade 3 thrombocytopenia; may restart at 1 dose level lower (refer to Table 5)
Non-Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Subsequenta	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (refer to Table 3)

Table 3. Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction[a,b]	Occurrence	Dose Modification for MCL and MZL After Recovery Starting Dose = 560 mg
Grade 2 cardiac failure	First	Restart at 420 mg daily[c]
	Second	Restart at 280 mg daily[c]
	Third	Discontinue IBRUTINIB
Grade 3 cardiac arrhythmias	First	Restart at 420 mg daily[c]
	Second	Discontinue IBRUTINIB
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue IBRUTINIB
Other Grade 3 or 4 non-hematological toxicities[d] Grade 3 or 4 neutropenia with infection or fever Grade 4 hematological toxicities	First	Restart at 420 mg daily
	Second	Restart at 280 mg daily
	Third	Discontinue IBRUTINIB

[a] See *Warnings and Precautions.*

[b] Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria, or International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for hematologic toxicities in CLL/SLL.

[c] Evaluate the benefit-risk before resuming treatment.

[d] For Grade 4 non-hematologic toxicities, evaluate the benefit-risk before resuming treatment.

These updated dosage modification recommendations may reduce the occurrence of additional serious events and are intended to improve tolerability for continued Imbruvica treatment.

Table 4. Ibrutinib Dose Reduction Levels

Starting Dose Level	560 mg
Dose Reduction Level 1	420 mg
Dose Reduction Level 2	280 mg
Dose Reduction Level 3	Discontinue

5.4.2 Dose Modification for Hepatic Impaired Subjects

Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines (Section 5.6.2.1). Ibrutinib is metabolized in the liver and therefore subjects with clinically significant chronic hepatic impairment at the time of Screening (Child- Pugh class B or C) are excluded from study participation. In the population PK analysis (1,202 subjects), 179 subjects (14.9%) had mild hepatic impairment according to National Cancer Institute criteria and 12 subjects (1.0%) had moderate hepatic impairment. These subjects did not show a significantly higher ibrutinib exposure compared with subjects with normal hepatic function. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. Refer to Appendix 6. Child-Pugh Scorefor Child-Pugh classification.

Obinutuzumab:

There is no dose reduction for Obinutuzumab; only infusion rate adjustment or discontinuation.

5.5 Study Product Accountability

Each site will maintain the study drug accountability for each drug using DARF forms.

5.5.1 Receipt of Drug Supplies

Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.5.2 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

5.6 Assessing Participant Compliance with Study Product Administration

Ibrutinib: The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit.

Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be re-dispensed to anyone. (see Patient Medication Diary).

Obinutuzumab will be administered by IV infusion in the hospital or outpatient setting.

If a patient does not wish to receive the infusions anymore, they will be discontinued from the study or may continue monotherapy with Ibrutinib at the discretion of the treating physician.

5.7 Concomitant Medications/Treatments

Concomitant therapy includes any prescription medications or over the counter preparations used by a patient between the 14 days preceding the study entry evaluation and the early study treatment termination visit/study treatment completion visit. All concomitant medications should be recorded at each visit for the entire duration that the patient is on the study and reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF).

5.7.1 Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. See section 5.2.3

After consultation with the investigator, the following may be considered: Localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

Steroids: Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (eg., joint inflammation, asthma exacerbataion, rash, anti-emetic use and infusion reactions) at doses that do not exceed 1000 mg per day of prednisone or equivalent are permitted.

Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100mg per day of prednisone or equivalent.

Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100mg per day of prednisone or equivalent.

5.7.2 Hormonal Therapy and Oral Contraceptives

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Effective contraception is required while receiving the study drugs. For women, effective contraception is required to continue for ≥18 months after the last dose of Obinutuzumab. For men, effective contraception is required to continue for ≥180 days after the last dose of Obinutuzumab.

5.7.3 Drugs That May Have Their Plasma Concentrations Altered By Ibrutinib

In vitro studies indicated that inbrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available; therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

5.7.4 **QT Prolonging Agents**

Any medications known to cause QT prolongation should be used with caution; periodic electrocardiogram (ECG) and electrolyte monitoring should be considered.

5.7.5 **Antiplatelet Agents & Anticoagulants**

Use Ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Ibrutinib should be held at least 3 to 7 days pre- and post- surgery depending upon the type of surgery and the risk of bleeding (see section 5.7.8). Subjects with congenital bleeding diathesis have not been studied.

5.7.6 **CYP3A – Inhibitors/Inducers**

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib with drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure. Avoid grapefruit and Sevile oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A. Dose adjustment of ibrutinib due to concomitant use of CYP3A inhibitors should follow Table 4.

Table 5. Ibrutinib Dose Modification Guidance for Co-Administration with CYP3A Inhibitors

Patient Population	Co-administered Drug	Recommended Ibrutinib Dose for the Duration of the Inhibitor Use[a]
B-Cell Malignancies	Mild CYP3A inhibitors	420 mg or 560 mg once daily per indication. No dose adjustment required.
	Moderate CYP3A inhibitors	280 mg once daily.
	Voriconazole 200 mg twice daily Posaconazole suspension 100mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily.
	Other strong CYP3A inhibitors Posaconazole at higher doses[b]	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

Monitor for adverse reactions to Ibrutinib and interrupt or modify dose as recommended (see Dosage and Administration)

After discontinuation of CYP3A inhibitor, resume previous dose of ibrutinib

- Avoid concomitant use of strong CYP3A inducers (eg., carbamazepine, rifampin, phenytoin, and St.John's Wort). Consider alternative agents with less CYP3A induction.
- A list of common CYP3A inhibitors and inducers is provided in Appendix 5. A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.
- For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

5.7.7 Excluded Therapy

- Any non-study protocol related chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment.

- Corticosteroids for the treatment of the underlying disease is prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100 mg of prednisone or its equivalent are prohibited.
- Use of Erythropoietin growth factors (eg., Epoetin alfa/ darbepoietin alfa) is prohibited.
- The use of live viral vaccines is contraindicated.
- The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.
- Refer to section 5.7.6 for use of CYP3A inhibitors/inducers and section 5.7.5 regarding use of anticoagulants.

5.7.8 **Procedures**

Ibrutinib may increase risk of bleeding with invasive procedures of surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period of subjects who require surgical intervention or an invasive procedure while receiving ibrutinib.

5.7.8.1 ***Minor Surgical Procedures***

For minor procedures (such as a central line placement, needle biopsy, thoracentesis or paracentesis) ibrutinib 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, it is not necessary to hold ibrutinib for these procedures.

5.7.8.2 ***Major Surgical Procedures***

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention (except for emergency procedures) 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 serosanguineous drainage or the need for drainage tubes.

5.8 **Dietary Restrictions**

Grapefruit and Seville oranges should be avoided for the duration of the study.

5.9 **Administration of Procedural Intervention**

5.9.1 **Premedication Requirements:**

Since some patients may develop hypersensitivity or other infusion related reactions (IRRs) to obinutuzmab, pre-medication is recommended to reduce the risk of infusion reaction as outlined below in Table 3. Closely monitor patients during the entire infusion. IRRs within 24 hours of receiving obinutuzumab have occurred.

For patients with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period since they may be at a greater risk of experiencing more severe reactions. Hypotension may occur as part of the obinutuzumab infusion reaction. Consider withholding antihypertensive treatments for 12 hours prior to, during each obinutuzumab infusion, and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their antihypertensive medication as is suggested here.

- Cycle 1 Day 1:

All patients requires pre-medication with IV glucocorticoid: dexamethasone (20mg) or methylprednisolone (80mg) administered at least one hour prior to obinituzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

An oral acetaminophen (975mg if available, 650-1000mg allowed per USPI) and an antihistamine such as diphenhydramine (50mg) administered at least 30 minutes before starting each obinutuzumab infusion.

- Cycle 1 Days 8 & 15 and Cycles 2-6 Day 1:

All patients requiring pre-medication with oral acetaminophen (975mg if available, 650-1000mg allowed per USPI), should have it administered at least 30 minutes before starting each obinutuzumab infusion.

Patients who experience an IRR (Grade 1 or more) with the previous infusion will require pre-medication with an antihistamine such as diphenhydramine (50mg) administered at least 30 minutes before starting each subsequent obinutuzumab infusion.

Patients who experience a Grade 3 IRR with the previous infusion will require pre-medication with IV glucocorticoid: dexamethasone (20mg) or methylprednisolone (80mg) administered at least one hour prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

Hypotension may be expected to occur during obinutuzumab infusions. Withholding of antihypertensive treatment 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 hypertensive medication.

Table 6. Premedication for Obinutuzumab

Day of Treatment Cycle	Patients requiring Premedication	Premedication	Administration
Cycle 1: Day 1	All patients	Intravenous	Completed at least 1 hour prior to obinutuzumab infusion
		Oral analgesic / anti-pyretic	At least 30 min before obinutuzumab infusion
		Anti-histamine drug	
All subsequent infusions	Patients with no IRR during the previous infusion	Oral analgesic/anti-pyretic	At least 30 minutes before obinutuzumab infusion
	Patients with an IRR (Grade 1 or 2 with the previous infusion)	Oral analgesic/anti-pyretic [2]	
		Anti-histamine drug[3]	
	Patients with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25x10^9/L prior to next treatment	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
		Anti-histamine drug[3]	

[1] 100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions

[2] e.g. 975 mg acetaminophen/paracetamol if available, 650-1000mg allowed per USPI.

[3] e.g. 50 mg diphenhydramine.

For TLS prophylaxis, see Section 5.2.3.1.

Treatment:

Ibrutinib

- Dose 560mg (4x 140mg capsules) orally once daily on days 1-28 until disease progression
- Premedication is not required for ibrutinib administration
- Full administration guidelines are outlined in Section 5.5.1.1 below
- Patients on ibrutinib should keep a daily drug administration record with dates and times taken (see Appendix 4, Patient Medical Diary)
- Dose modifications/dose delays after cycle 1 are outlined in section 5.10

Obinutuzumab

- Obinutuzumab 1000mg will be administered by IV infusion.

Induction:

- On Cycle 1, Days 1, 8, and 15, 1000mg obinutuzumab will be administered
- On Cycles 2-6, Day 1, 1000mg obinutuzumab will be administered

Maintenance: Patients with at least a partial response after cycle 7 will continue to receive maintenance therapy as follows: 1000mg of obinutuzumab will be administered to start 2 months after finishing cycle 6 and will be given every 2 months for a total of 12 doses (see Table 2).

Full administration guidelines are outlined in section 5.9

Table 7 Obinutuzumab Dosing Schedule

<table>
<tr><th colspan="2">Cycle and Day of Administration</th><th>Dose of Obinutuzumab</th><th>Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)</th></tr>
<tr><td rowspan="3">Cycle 1</td><td>Day 1</td><td>1000 mg</td><td>Administer at 50 mg/hr. The rate of the infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.</td></tr>
<tr><td>Day 8</td><td>1000 mg</td><td rowspan="3">If no infusion reaction occurred during the previous infusion and</td></tr>
<tr><td>Day 15</td><td>1000 mg</td></tr>
<tr><td>Cycles 2–6</td><td>Day 1</td><td>1000 mg</td></tr>
</table>

Maintenance	Every 2 months (starting 2 months after cycle 6) for 12 doses	1000 mg	the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Dose modifications/dose delays after cycle 1 are outlined in Section 5.10

Dosage Modification/Toxicity Management

Consider treatment interruption if a patient experiences an infection, Grade 3 or 4 cytopenia, or a ≥ Grade 2 non-hematologic toxicity.

5.9.2 **Infusion Related Reactions**

Institute medical management (e.g., glucocorticoids, subcutaneous epinephrine, bronchodilators, and/or oxygen) for IRRs as needed. Resuscitation equipment should be available for immediate use. If a patient experiences an IRR of any grade during infusion, adjust the infusion as follows:

- Grade 4 (life-threatening including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction): Stop infusion immediately and permanently discontinue obinutuzumab therapy. Patients should be observed in the hospital for 24 hours after a grade 3-4 infusion reaction

- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any further infusion-reaction symptoms, the infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose. Permanently discontinue treatment if a patient experiences a Grade 3 infusion-related symptom at re-challenge.

- Grade 1 □ 2 (mild to moderate): Reduce the infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if the patient does not experience any further infusion-reaction symptoms, infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose.

Life-Threatening Infusion-Related Reactions and Anaphylaxis

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional obinutuzumab should be administered. Patients who experience any of these reactions should receive aggressive treatment of symptoms and will be discontinued from study treatment.

5.10 Supportive Care and Prophylactic Medications:

Prophylaxis for Tumor Lysis Syndrome (TLS):

All patients with bulky lymphadenopathy (per GELF criteria, see Appendix 1), peripheral blood lymphocytes $\geq 25x10^9$/L, and patients with renal impairment must receive prophylaxis for TLS prior to the initiation of study treatment.

This includes appropriate hydration consisting of a fluid intake of approximately 3L/day starting 1-2 days prior to the first dose of obinutuzumab and administration of anti-hyperurimics (eg., allopurinol 300mg/day orally) starting 24 hours prior to the first infusion of obinutizumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment (twice weekly lab check for serum uric acid, serum phosphate level, serum creatinine, and serum potassium). Patients still considered at risk for TLS because of persistently high tumor burden before the second and subsequent infusions of obinutuzumab should continue TLS prophylaxis with allopurinol and adequate hydration until the risk is abated, as determined by the investigator. For patients with evidence of TLS, obinutuzumab should be discontinued and the patient treated as clinically indicated including correction of electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. Following the complete resolution of TLS complications, obinutuzumab may be re-administered at the full dose during the next infusion in conjunction with prophylactic therapy.

Infections Prophylaxis

Patients with Grade 3 to 4 neutropenia lasting more than one week are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered.

Supportive Care

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics etc., when appropriate. All blood products should be irradiated and leukopore filtered to prevent transfusion-associated graft versus host disease.

Erythropoietin growth factors (eg., Epoetin Alfa/Darbepoietin Alfa). Use of epoetin alfa/darbepoietin alfa in this protocol is prohibited.

Filgastrim (G-CSF), pegfilgastrim and sargramostim (GM-CSF): Filgastrim (G-CSF), pegfilgastrim and sargramostim treatment is allowed per ASCO guidelines but not encouraged. Filgastrim pegfilgastrim and sargramostim: may not be used prophylactically to avoid dose reductions or delays. For the treatment of febrile neutropenia the use of colony-stimulating factors (CSFs) should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction

(sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. If filgastrim/pegfilgastrim or sargramostim are used, they must be obtained from commercial sources.

Hepatitis B Management

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with obinutuzumab.

Positive serology for Hepatitis B is defined as positivity for Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (anti-HBc). Patients who are positive for anti-HBc at screening, may be considered for inclusion in the study if they are Hepatitis B viral DNA negative, are willing to undergo HBV DNA testing by real-time PCR approximately every 4 weeks, and will receive appropriate anti-hepatitis B viral suppression therapy. These patients should be referred to a hepatologist or gastroenterologist for appropriate monitoring and management.

Patients who experience reactivation of hepatitis B DNA (>100 IU/ml) while on antiviral Hepatitis B suppression therapy will be withdrawn from the study. These patients should be referred to a hepatologist immediately to institute appropriate treatment.

Patients who are carriers of hepatitis B (positive hepatitis B core antibody) at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis.

5.11 Procedures for Training of Clinicians on Procedural Intervention

N/A

5.12 Assessment of Clinician and/or Participant Compliance with Study Procedural Intervention

The first dose of ibrutinib will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. The ibrutinib will be dispensed to subjects in bottles at each visit. Unused drugs dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be redispensed to anyone. We will record the compliance of the pills via the use of a pill diary (See Appendix 4).

Obinutuzumab will be administered in the clinic or hospital intravenously. If the patient misses a dose, we will proceed with giving the missed dose as soon as possible.

The TJU Clinical Trial Management System will be used to track patient enrollment and screening information for all patients enrolled in this study at Thomas Jefferson University. No other database systems will be utilized to track patient data for this study.

6 Study Schedule

Please refer to Appendix 2 for a complete study schedule.

Screening/Enrollment/Baseline assessments

All patients who may be eligible for this study will be screened by the PI or a co-investigator and, if eligible, will be asked to participate in this study by signing a consent form. Once the consent form is signed the following schedule will take effect. Laboratory and clinical parameters during the treatment courses are to be followed using individual institutional guidelines and the best clinical judgement of the responsible physician. It is expected the patients on this protocol will be cared for by physicians experienced in the treatment and supportive care of patients with lymphoma.

6.1.1 To be completed within 7 weeks (49 days) before enrollment:

1. Pathological confirmation of indolent lymphoma as outlined in inclusion criteria.
2. Staging bone marrow biopsy with flow cytometry.
3. FISH studies on tissue involved with lymphoma (bone marrow or lymph node or tissue biopsy)
4. PET/CT scan. CT scan can be done instead of PET/CT if unable to obtain PET/CT. Magnetic resonance imaging may be used instead of CT or PET/CT when CT with contrast or PET/CT is medically contraindicated.

6.1.2. To be completed within 30 DAYS before enrollment:

1. Documentation of informed consent.
2. Review patient concomitant medications list as outlined in section 5.7.
3. Hepatitis B (surface antigen, surface antibody, core antibody). Patients with a positive core antibody and a negative surface antibody should be tested for hepatitis B viral load with PCR.
4. Hepatitis C (antibody). Hepatitis C viral PCR if positive serology.
5. HTLV-1 serology.

6.1.3. To be completed within 14 days prior to first dose of study drug:

1. History and physical examination including vital signs, blood pressure, performance status and tumor assessment.

2. Review patient's concomitant medications list as outlined in sections 5.7
3. Document what is the indication for treatment
4. Blood work including complete blood count (CBC) with differential, complete metabolic panel, PT/INR/PTT, LDH, uric acid, magnesium, and phosphorus.
5. Pregnancy test (serum or urine B-HCG) for women of childbearing potential. A negative serum pregnancy test should be done within 72 hours prior to initiating protocol therapy and be practicing an effective form of contraception during protocol therapy and for at least 18 months following completion of Obinutuzumab.

6.1 Treatment/Maintenance Period & End of Treatment

1. Cycle 1:

i. Cycle 1 Day 1:

i. History and physical exam including vital signs and ECOG performance status.

ii. Labs: CBC with differential, CMP (sodium potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST and alkaline phosphatase), uric acid, LDH, phosphorus, magnesium, coagulation panel (PT/INR/PTT).

iii. Record the concomitant medications that patient has been taking

iv. If female of child bearing potential, perform serum or urine pregnancy test

v. Record any baseline adverse events

vi. Dispense and administer Ibrutinib 560 mg PO

vii. Administer Obinutuzumab 1000mg IV infusion

ii. Cycle 1 Day 2:

i. Record any concomitant medications

ii. Labs Day 2: tumor lysis labs (potassium, sodium, BUN, creatinine, uric acid, LDH, phosphate) for patients at high risk of TLS as assessed by the investigator.

iii. Cycle 1 Day 8:

i. Labs: CBC with differential, CMP (sodium potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST and alkaline phosphatase), uric acid, LDH, phosphorus, magnesium, coagulation panel (PT/INR/PTT).

ii. Administer – Obinutuzumab 1000 mg IV infusion

iv. Cycle 1 Day 15 (±3 days):

i. History and physical exam including vital signs and ECOG performance status.

ii. Record any concomitant medications

iii. Record the adverse events

iv. Labs: CBC with differential, CMP (sodium potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST and alkaline phosphatase), uric acid, LDH, phosphorus, magnesium, coagulation panel (PT/INR/PTT).

v. Administer – Obinutuzumab 1000 mg IV infusion

v. Cycle 1 Day 22:

i. Labs CBC with differential, CMP (sodium potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST and alkaline phosphatase), uric acid, LDH, phosphorus, magnesium, coagulation panel (PT/INR/PTT).

2. To be done during Cycle 2 through Cycle 6:

i. Day 1 of each cycle, perform history and physical exam including vital signs and ECOG performance status

ii. Day 1 of each cycle, complete labs: CBC with differential, CMP (sodium potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST and alkaline phosphatase), uric acid, LDH, phosphorus, magnesium, coagulation panel (PT/INR/PTT).

iii. On Day 1 of each cycle, record concomitant medications

iv. On Day 1 of each cycle, record any adverse events

v. Day 1 of each cycle: administration of Obinutuzumab 1000mg IV infusion

vi. After completion of cycle 4, PET/CT scan or CT scan (recommended halfway through cycle 5).

3. To be done during Cycle 7 until 5 years:

i. Patients with at least a partial response will continue to receive maintenance therapy as follows: 1000mg of obinutuzumab to start 2 months after cycle 6 (aka “cycle 8”) and will be given every 2 months for a total of 12 doses (2 years).

ii. History and physical every 2 months for the first year, then Q4 months for the second year of maintenance therapy and then every 6 months until 5 years post-enrollment.

iii. Perform labs at least Q2 months for the first year, then Q4 months for the second year of maintenance therapy; after the completion of second year, labs every 6 months until 5 years after enrollment. [Labs include CBC with differential, CMP (sodium potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST and alkaline phosphatase), uric acid, LDH, phosphorus, magnesium, coagulation panel (PT/INR/PTT)]. Labs may be performed more frequently if clinically indicated.

iv. Record adverse events at the same timepoints noted above for labs, and concomitant medications with office visits.

v. After the completion of cycle 7 (recommended halfway through cycle 8), PET/CT or CT scan and Q6 months then on for 2 years. Thereafter, PET/CT or CT scans to be done annually or as clinically indicated after the maintenance therapy is completed. Magnetic resonance imaging may be used instead of CT or PET/CT when CT with contrast or PET/CT is medically contraindicated.

6.2 End Of Study Procedures

1. Lymph node biopsy and/or bone marrow biopsy if clinically indicated
2. PET/CT scan or CT scan if clinically indicated. Magnetic resonance imaging may be used instead of CT or PET/CT when CT with contrast or PET/CT is medically contraindicated.
3. History and physical exam including vital signs and ECOG performance status
4. Labs CBC with differential, CMP (sodium potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST and alkaline phosphatase), uric acid, LDH, phosphorus, magnesium, coagulation panel (PT/INR/PTT).
5. Record adverse events and concomitant medications

6.3 Post-treatment Contraception

Female patients of reproductive potential who are not surgically sterile must practice adequate birth control for a minimum of 18 months post-treatment; male patients who are not surgically sterile must practice adequate birth control for a minimum of 180 days post-treatment.

6.4 Evaluation of Response

- Patients with evidence of progressive disease after cycle 4 will be regarded as treatment failure and withdrawn from the study. Patients with stable disease or progressive disease after cycle 7 will be regarded as treatment failure and withdrawn from the study.
- Patients with at least partial response after cycle 7 will continue therapy.

- Response to therapy will be assessed based on imaging after cycle 7. The revised Lugano criteria [22] will be used to assess response (see Appendix 9).

7 Study Procedures and Evaluations

7.1 Study Procedures/Evaluations

Assessments to be done during cycle 1 (day 1 to day 28):

1. Every 2 week physician visits for evaluation of toxicities
2. Day 2 tumor lysis labs (Potassium, Sodium, BUN, Creatinine, Uric acid, LDH, Phosphate) for patients with high risk of TLS as assessed by the investigator.
3. At least weekly labs including: Complete blood count (CBC) with differential, complete metabolic panel (CMP), PT/INR/PTT, LDH, Uric acid, Magnesium and Phosphorus
4. Review patient's concomitant medications list as outlined in section 5.7

Assessments to be done during Cycles 2-6:

1. At least monthly physician visits for evaluation of toxicities.
2. At least twice monthly labs including: complete blood count (CBC) with differential, complete metabolic panel, PT/INR/PTT, LDH, uric acid, magnesium and phosphorus.
3. PET/CT scan to assess for response to therapy after completion of Cycles 4 and Cycle 7. CT scan can be done instead of PET/CT if unable to obtain PET/CT. A bone marrow biopsy needs to be repeated any time necessary to confirm CR by imaging except in subjects with no evidence of lymphomatous marrow involvement performed during screening (see Appendix 9 for response criteria).
4. Review patient's concomitant medications list monthly.

Assessments to be done after completion of Cycle 7 until 5 years:

If patient has at least partial response to the treatment and wishes to continue, they can continue to receive maintenance therapy (1000mg obinutuzumab IV Q2months) along with Ibrutinib QD indefinitely.

1. Physician visits for evaluation of toxicities (every 2 months during 1st year of maintenance obinutuzumab, and then every 4 months during 2nd year of maintenance obinutuzumab, then every 6 months afterwards until year 5).

2. Labs: complete blood count (CBC) with differential, complete metabolic panel, PT/INR/PTT, LDH, uric acid, magnesium and phosphorus. Q2 months for the first year, then Q4 months for second year of maintenance therapy, then Q6 months till 5 years after enrollment.

3. PET/CT scan (preferred) or CT scan if unable to obtain PET/CT to assess for progression of disease every 6 months after Cycle 7 till 2 years. After second year, imaging PET/CT (or CT if unable to obtain PET/CT) annually or as needed if there is suspicion for relapsed disease.

4. Review patient's concomitant medications list with office visits.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Laboratory Measurements

- Blood samples: CBC with differential, CMP, PT/INR/PTT, LDH, uric acid, Magnesium, and Phosphorous, pregnancy test (serum or urin B-HCP) for women of child bearing potential, potassium, sodium, BUN, creatinine, phosphate, Hep B (surface antigen, surface antibody, core antibody), Hep B viral load with PCR (as needed), Hep C (antibody), Hep C viral PCR (as needed), HTLV-1 serology (see Appendix A, Schedule of Assessments).

7.2.2 Special Assays or Procedures

N/A

7.2.3 Specimen Preparation, Handling, and Storage

All biological specimens will be de-identified and labeled with only the patient's enrollment number and sample collection date.

See laboratory manual for additional information.

7.2.4 Specimen Shipment

8 Evaluation of Safety

8.1 Specification of Safety Parameters

8.1.1 Unanticipated Problems

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.2 **Adverse Events**

An adverse event is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

For the purpose of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term "disease progression" should not be reported as an adverse even term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with follicular or marginal zone lymphoma that were not present prior to the AE reporting period
- Subjective or objective symptoms provided by the subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance
- Any AEs experienced by the subject through the completion of final study procedures
- Complications that occur as a result of protocol-mandated interventions (eg., invasive procedures such as cardiac catheterization)
- 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.

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test procedures should be reported.

8.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical

judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition.

8.2 Safety Assessment and Follow-Up

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 FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all 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 the study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, 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 (see following guidance), and actions taken.

Events will be followed for outcome information until resolution or stabilization.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.2.1 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity

- The abnormality is of a degree that requires active management eg., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation etc.

8.2.2 **Hospitalization, Prolonged Hospitalization or Surgery**

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

All AEs, whether serious or non-serious, will be captured from the time signed and dated ICF is obtained until 30 days following the last dose of study drug.

Serious adverse events reported after 30 days following last dose of study drug should also be reported if considered related to the study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an even term, but instead symptom/clinical signs of disease progression may be reported.

All adverse events, regardless of seriousness, severity or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator’s evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”).

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

8.2.3 **Pregnancy**

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the investigator if she becomes pregnant from the time of consent to 18 months after the last dose of study drug. A male subject must immediately inform the investigator if his partner becomes pregnant from the time of consent to 180 days after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. If a female subject becomes pregnant while receiving the study drug or within 18 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 180 days must be reported to Pharmacyclics and Genentech Drug Safety or designee, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old and this must be reported to Pharmacyclics and Genentech Drug Safety, or designee, per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

8.2.4 **Other Malignancies**

All new malignant tumors including solid tumors, skin malignancies, and hematologic malignancies will be reported for the duration of the study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed enter data in the corresponding eCRF.

8.2.5 **Eye-Related Adverse Events**

New or worsening eye-related symptoms that are Grade 2 or higher, or a symptom that was Grade 2 or higher at baseline worsens, should be evaluated by an ophthalmologist whose findings should be reported on the ophthalmologic eCRF.

8.2.6 **Adverse Events of Special Interest (AESI)**

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to Pharmacyclics and Genentech Drug Safety per the SAE reporting timelines.

8.2.7 **Major Hemorrhage**

Major hemorrhage is defined as any of the following:

1. Any treatment-emergent hemorrhagic adverse event of Grade 3 or higher*.
2. Any treatment-emergent serious adverse events of bleeding of any grade.
3. Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v5.0.

Events meeting the definition of major hemorrhage will be captured as an event of special interest.

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 $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
    - Treatment-emergent ALT or AST $> 3 \times$ 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

The Obinutuzumab Events of Special Interest are:

- All TLS (irrespective of seriousness, causality or severity)
- Second Malignancies

8.3 Recording Adverse Events

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

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

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 4 Safety Assessment and Follow-Up.

8.3.1 Relationship to Study Intervention

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

8.3.2 **Expectedness**

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

An "unexpected" AE is an AE that is not listed in the investigator's brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the investigator's brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the investigator's brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

All AEs and SAEs whether volunteered by the subject, discovered by the 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 or Ibrutinib (see following guidance) and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guidelines:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the Obinutuzumab or Ibrutinib, and the AE cannot be readily explained by the subject'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.

No

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

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current investigator brochure (IB).

Unexpected adverse events are those not listed in the PI or current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the PI or IB. For example, under this definition, hepatic necrosis would be unexpected if the PI 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.

8.3.3 **Severity of Event**

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v5.0, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment and not interfering with the subject's daily activities.
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are acceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

8.3.4 **Intervention**

Any intervention implemented to treat the adverse event must be documented for all adverse events.

8.4 **Safety Reporting**

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 FDA, appropriate IRB(s), and Genentech, Inc in accordance with CFR 312.32 (IND safety reports).

8.4.1 **Reporting to IRB**

8.4.1.1 ***Unanticipated Problems***

All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 8.1.1 Unanticipated Problems require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the IRB on an OHR-20 form via the eazUP system within 10 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the IRB at the next continuing review.

8.4.1.2 ***Adverse Events***

Grade 1 AEs will be reported to the IRB at the time of continuing review.

Grade 2 AEs will be reported to the IRB at the time of continuing review.

8.4.1.3 ***Serious Adverse Events***

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will be reported to the IRB within 5 working days.

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.

All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

8.4.2 **Reporting to SKCC DSMC**

All AEs and SAEs, safety and toxicity data, and any corrective actions will be submitted to the DSMC per the frequency described in the SKCC DSMP. The report to the SKCC DSMC will also include any unanticipated problems that in the opinion of the PI should be reported to the DSMC. The DSMC meets quarterly. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets

(by conference call) within 24 hours following the notification of an unexpected adverse event felt to be related to the study drug.

Prior to each DSMC meeting, each board member, is provided a printout of all reported AEs and SAEs occurring during the reporting period for this clinical trial. The principal investigator provides a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment, a written report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol, as well as recommendations from the Medical Monitor. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.

For expedited reporting requirements, see table below:

DSMC AE/SAE Reporting Requirements

	Grade 1	Grade 2		Grade 3				Grades 4 and 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I - 48 Hours (Death: 24 Hours) Phase II - 5 working days
Possible Probably Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase I - 48 Hours Phase II - 5 working days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I and Phase II - 48 Hours (Death: 24 Hours)

8.4.3 Specific Instructions for Recording Adverse Events to Genentech/Roche and Pharmacyclics

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

All serious adverse events and AEs of special interest (AESIs) (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email **(AEintakeCT@pcyc.com) or fax (408) 215-3500)** to Pharmacyclics Drug Safety Pharmacovigilance & Epidemiology (DSP&E), or designee, within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

Sponsor will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Obinutuzumab to Genentech within the timelines described below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

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

All Product Complaints *without* an AE should call via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

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

Type of Report	Timelines
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or

SAEs. Avoid colloquialisms and abbreviations.

8.4.3.1 *Diagnosis vs. Signs & Symptoms*

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (eg., 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.

8.4.3.2 *Deaths*

All deaths that occur during the protocol-specified AE reporting period (see section 8.2) 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 single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

8.4.3.3 *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 (eg., “more frequent headaches”).

8.4.3.4 *Hospitalizations for Medical and Surgical Procedures*

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

Hospitalization for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing 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

8.4.3.5 *Post-Study Adverse Events*

For studies involving collection of survival data and follow-up until progression free period the investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug) 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 study drug.

Case Transmission Verification will be performed by both parties (Sponsor & Genentech) during this period to ensure successful transmission of Single case reports.

8.4.3.6 *Reconciliation (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 Sponsor emailing Genentech a Quarterly line-listing documenting single case reports sent by Sponsor 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 Sponsor 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.

All serious adverse event that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject’s participation in the study, must be followed until any of the following occurs:

- The event resolves

- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors related to the study
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to followup after demonstration of due diligence with followup efforts).

Aggregate Reports

IND ANNUAL 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 mailbox: ctvist_drugsafety@gene.com

Other Reports

Thomas Jefferson University will forward a copy of the publication to Genentech/Roche upon completion of the study.

8.4.4 Reporting to Regulatory Authorities, Ethics Committees and Investigators

Thomas Jefferson 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.

Thomas Jefferson University will be responsible for the expedited reporting of safety reports originating from the Study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB) of the Concerned Member States, where applicable.

Thomas Jefferson University as the Sponsor of the Study, will be responsible for the preparation of six-monthly Suspected Unexpected Serious Adverse Reaction (SUSAR) reports and their submission to Investigators, Regulatory Authorities and the Institutional Review Board/Independent Ethics Committee (IRB/IEC), where applicable.

Thomas Jefferson University will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

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 21CFR §600.80.

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidelines 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 (Ibrutinib and Obinutuzumab). An unexpected adverse event is one that is not described in the Ibrutinib and Obinutuzumab investigator brochure. Such reports are to be telephoned or faxed to the FDA and Genentech/Roche 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 (Ibrutinib and Obinutuzumab). An unexpected adverse event is one that is not already described in the (Ibrutinib and 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/Roche, 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: 1(800)FDA 0178

All written IND Safety Reports submitted to the FDA by the investigator must also be sent to Genentech/Roche Drug Safety:

Fax: (650)255-4682 or (650)225-4630

Email: usds_aereporting-d@gene.com

And Pharmacyclics Fax: (408)215-3372

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

Tel: (888) 835-2555

Fax: (650)255-4682 or (650)225-4630

IND ANNUAL REPORTS:
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech and Pharmacyclics.

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

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:

- Email: ga101-gsur@gene.com
- Fax: 866-706-3927
- And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES:

Queries related to the study will be answered by Thomas Jefferson University. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Sponsor and Genentech/Roche. Genentech will work collaboratively with the Sponsor-Investigator on queries but Genentech/Roche shall have the final say and control over safety queries relating to Obinutuzumab. Thomas Jefferson University agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Obinutuzumab independently but shall redirect such queries to Genentech/Roche.

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.

SIGNAL MANAGEMENT AND RISK MANAGEMENT

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that Thomas Jefferson University**,** as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If Thomas Jefferson University issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Roche within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist Thomas Jefferson University with signal and risk management activities related to the Product within the Study.

Genentech will also provide Thomas Jefferson University with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

COMPLIANCE WITH PHARMACOVIGILANCE AGREEMENT / AUDIT

The Parties shall follow their own procedures for adherence to AE reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding AE report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding AE reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

SAFEY CRISIS MANAGEMENT

In case of a safety crisis, eg., 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 Obinutuzumab is used, or where there is media involvement, the Sponsor and Genentech/Roche agree to contact each other as soon as possible, based on where the crisis originates.

Genentech/Roche and the Sponsor will work collaboratively but Genentech/Roche shall have the final say and control over safety crisis management issues relating to Obinutuzumab. Thomas Jefferson University agrees that it shall not answer such queries from media and other sources relating to Obinutuzumab but shall redirect such queries to Genentech/Roche.

8.4.5 Adverse Events of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring the Obinutuzumab:

- **Non drug Specific AESIs:**
  - Case 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 and based on the following observations: Treatment-emergent ALT or AST>3xbaseline value in combination with total bilirubin >2xULN (of which >35% is direct bilirubin)-Treatment-emergent ALT or AST >3xbaseline value in combination with clinical jaundice.
  - Suspected transmission of an infectious agent by the study treatment, as defined below- Any organism, virus, or infectious particle (eg., 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 study treatment is suspected.
- **AESIs specific to Gazyya (Obinutuzumab):**
  - Tumor lysis syndrome (serious and non-serious)
  - Second Malignancy

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

- Date related to Obinutuzumab 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

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.

8.4.6 Reporting of Pregnancy

If a female subject becomes pregnant while receiving Obinutuzumab or 18 months after the last dose of Obinutuzumab, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 180 days after the last dose of Obinutuzumab, a report should be completed and expeditiously submitted to 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 subject exposed to the study drugs should be reported as an SAE.

8.5 Halting Rules

Per the IST Contract, the investigator reserves the right to terminate the study at any time. Should this be necessary, both the investigator will arrange discontinuation procedures in partnership with Pharmacyclics or Genentech. In terminating the study, the investigator will assure that adequate consideration is given to the protection of the subjects' interests. Pharmacyclics or Genentech may terminate the study for reasons including, but not limited to evidence that the PI or an involved investigator is unqualified to conduct research or fulfill sponsor responsibilities (eg., listed on a debarment or ineligible investigator list); failure to meet timelines or achieve agreed upon milestones; a known or perceived risk to patient well-being is identified; or breach of contract. Additional grounds for termination are outlined in the IST agreement.

8.6 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

8.7 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 (ie., DOB, 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).

Occasionally, Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported.

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

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

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at:

https://www.fda.gov/media/69876/download

9 Study Oversight

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC). The SKCC DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the NCI.

10 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SKCC DSMP.

10.1 **Study Monitoring Plan**

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Phase II studies require monthly monitoring by the PI of the study with quarterly safety and monitoring reports submitted to the CRO, and the DSMC. Each protocol is assigned to a medical monitor (a physician or other member of the DSMC who has expertise in the therapeutic area of the protocol and is not directly involved in this trial). The medical monitor reviews all adverse events (in addition to unexpected adverse events), safety data and activity data observed in the ongoing clinical trial.

The PI provides a report to the DSMC of all AEs/SAEs, safety and toxicity data, and any corrective action that occurred on a quarterly basis. The medical monitor also provides a summary of their review. The summary of all discussions of adverse events are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place quarterly. Patients are only identified by initials, and no other PHI is included in the reports.

The medical monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data observed throughout the life of a clinical trial. In such circumstances, an "ad hoc" DSMC meeting will be called to discuss corrective action with the PI.

The summary of all discussions of adverse events are included in the SKCC Investigator's reports to the TJU IRBs as part of its annual progress report. The DSMC and the TJU IRB may, based on the monitor's recommendation, suspend or terminate the study. The quarterly safety and monitoring reports include a statement as to whether this data has invoked any stopping criteria in the clinical protocol.

10.2 Auditing & Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the funding sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (eg., pharmacy, diagnostic laboratory etc.)

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

Independent External & Internal Audits:

In addition to review by the DSMC, all studies initiated by SKCC investigators are audited by an independent auditor once they have achieved 10% of target accrual. However, a study can be audited at any time based on recommendations by the IRB, DSMC, PRC and/or the SKCC Studies are re-audited once they have achieved 50% of target accrual. Special audits may be recommended by the IRB, DSMC or PRC based on prior findings, allegations of scientific misconduct and where significant irregularities are found through quality control procedures.

Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10 and 50%, the CRO randomly audits at least 10% of all patients entered into therapeutic SKCC trials and other trials as necessary, on at least a biannual basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

All audit reports are submitted to the DSMC for review and action (when appropriate). A copy of this report and recommended DSMC action is sent to the PRC and TJU IRB. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist the PIs in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The TJU IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

11 Statistical Considerations

11.1 Sample Size Determination

Single arm, 2 stage Simon design. This is a nonrandomized, single arm, open label Phase II trial designed to evaluate the efficacy of the combination of ibrutinib and obinutuzumab in previously untreated patients with indolent non-Hodgkin's lymphoma. This combination would

be an alternative to standard chemotherapy with considerably less adverse effects and a similar or better efficacy profile. Since this is a single arm study, the overall response will be compared to historical overall responses reported in the literature to be about 70%. As this combination has not been evaluated previously, we designed this trial with the potential for early termination in the case of a poor overall response. The design will be a two-stage design using the method of Simon, augmented with admissible choices. The choice of design is guided by a desire to stop the trial early if the actual overall response rate is 0.4 or less. If the overall response rate is 0.68 or greater, we would like to have a low probability of failing to conclude efficacy. After testing the combination in 12 patients in the first stage, the trial will be terminated if 5 or fewer respond. If the trial goes on to the second stage, a total of 30 patients will be studied. If the total number responding is less than or equal to 16, the combination is rejected. Our chosen optimal design is such that if the drug combination is actually not effective, there is a 0.042 probability of concluding that it is (the target for this value was 0.05). If the drug is actually effective, there is a 0.098 probability of concluding that it is not (the target for this value was 0.1). If the actual overall response rate is 0.4 or worse, we have at least a 0.665 probability that the trial will stop after the first 12 subjects.

Number of patients after which review needs to be done	Stop if the number of successes is less than or equal to
12	5
Number of patients after which review needs to be done	Stop if the number of successes is less than or equal to
30	16

11.2 **Statistical Methods**

The primary endpoint is overall response rate (ORR evaluated after 7 cycles of treatment). Secondary endpoints are partial remission or complete remission (PR/CR), progression-free survival (PFS), overall survival (OS), as well as grade ¾ toxicity. We will compute estimates of response and toxicity rates, along with the corresponding confidence intervals, using appropriate exact methods that take into account the 2-stage design. The Kaplan-Meier method will be used to estimate PFS and OS.

11.3 **Subject Population(s) for Analysis**

As described in section 4.5, we will document the reason for withdrawal from the study. If a patient withdraws (or is withdrawn) from the study due to non-compliance they will be replaced. However, if a patient withdraws from the study after having started treatment due to either

toxicity, lack of tolerance or lack of confidence on the effectiveness of the regimen, they will be retained in the study and we will make every effort to obtain efficacy and toxicity data. These patients will be included in the final analysis.

12 Source Documents and Access to Source Data/Documents

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

13 Quality Control and Quality Assurance

The investigator will allocate adequate time for monitoring activities. The investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all of the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.) and has adequate space to conduct the monitoring visit.

14 Ethics/Protection of Human Participants

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study. All subjects for this study will be provided a consent form that is compliant with local and federal regulations, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

This study is only designed for adults and thus all patients below (but not including) the age of 18 years are excluded from this study. There is no limitation on the inclusion of patients with respect to gender and race/ethnicity. However, women who are pregnant or nursing will be excluded due to potential of birth defects which may be caused by the study drug. Men are overrepresented in non-Hodgkin lymphoma and the male:female ratio is approximately 3:1. The enrollment of women will be monitored quarterly.

14.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

14.6 Future Use of Stored Specimens and Other Identifiable Data

Samples will be stored with a unique identifier.

15 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents must be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

15.1 Source Documents

Source data is all information, original records, of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

15.2 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

15.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

15.4 Data Capture Methods

Data will be captured on paper case report forms and transferred to an electronic database which will be kept behind a password protected firewall database. Only the Principal Investigator and the research team members will have access to the data.

15.5 Types of Data

Data that will be collected include patient history and physical examination data, safety, laboratory studies, pathology studies, treatment, diagnostic imaging, and immunohistochemistry as determined in the laboratory.

15.6 Study Records Retention

The study essential documents will be retained for at least 2 years after the last documented one year follow-up for the last patient enrolled on this study.

15.7 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB and other regulatory bodies according to their requirements.

16 Study Finances

16.1 Funding Source

This study will be considered supported by the Thomas Jefferson University Department of Medical Oncology and through an award from the Sidney Kimmel Cancer Center.

The investigational products are being provided by Pharmacyclics and Genentech/Roche.

16.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict

reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

We have no conflict of interest in this study.

16.3 Participant Stipends or Payments

Participants will not receive payment for participation in the study.

17 Publication and Data Sharing Policy

Per the IST Agreement, the Investigator is required to submit to Pharmacyclics and Genentech a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. Pharmacyclics or Genentech may provide scientific comments and suggestions understanding that the Investigator has sole editorial responsibility, and retains the authority to make the final determination on whether or not to incorporate Pharmacyclics or Genentech comments or requests for additional information.

18 Literature References

1. Federico, M., et al., R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol, 2013. 31(12): p. 1506-13.

2. Rummel, M.J., et al., Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet, 2013. 381(9873): p. 1203-10.

3. Flinn, I.W., et al., Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood, 2014. 123(19): p. 2944-52.

4. Dal Porto, J.M., et al., *B cell antigen receptor signaling 101.* Mol Immunol, 2004. 41(6-7): p. 599- 613.

5. Bernal, A., et al., Survival of leukemic B cells promoted by engagement of the antigen receptor. Blood, 2001. 98(10): p. 3050-7.

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15. Fowler, N., et al., Ibrutinib Plus Rituximab in Treatment-Naive Patients with Follicular Lymphoma: Results from a Multicenter, Phase 2 Study. Blood, 2015. 126(23): p. 470-470.

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18. Alduaij, W., et al., Novel type II anti-CD20 monoclonal antibody (GA101) evokes homotypic adhesion and actin-dependent, lysosome-mediated cell death in B-cell malignancies. Blood, 2011. 117(17): p. 4519-29.

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22. Cheson, B.D., et al., Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol, 2014. 32(27): p. 3059-68.

SUPPLEMENTAL MATERIALS

The following documents are officially affiliated with the protocol and will be submitted to the IRB as a part of the protocol. As such, changes to these items require a protocol amendment.

Appendix 1. GELF criteria*

Appendix 2. Schedule of Assessments

Appendix 3. ECOG Status Scores

Appendix 4. Inhibitors and Inducers of CYP3A

Appendix 5. Child-Pugh Score

Appendix 6. Modified Ann Arbor Staging System

Appendix 7: Revised Criteria for Response Assessment

Appendix 1. GELF criteria*

Involvement of ≥3 nodal sites, each with a diameter of ≥3cms

Any nodal or extra nodal tumor mass with a diameter of ≥7cms

B symptoms

Pleural effusions or peritoneal ascites

Cytopenias (leukocytes < 1.0 x 10^9/L and/or platelets <100x10^9/L

Leukemia (>5.0 x 10^9/L malignant cells)

Symptoms attributable to lymphoma

Threatened end-organ function

*Solal Celgny P, Lepage E, Brousse N, et al. Doxorubicin containing regimen with or without containing interferon alpha 2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des lymphomes Folliculaire 86 trial. J Clin Oncol 1998; 16: 2332-23.

Appendix 2. Schedule of Assessments

Study Visits	Screening			Treatment Phase (1 cycle = 28 days)								Suspected PD
				Cycle 1					Cycles 2-6		Cycle 7 until 5 years	Any time
				D1	D2	D8	D15	D22	D1	D15		
Study Visit Windows	**-49 days****	**-30 days****	**-14 days**	**± 3 days**							**± 14 days**	Any time
Informed consent		X										
Lymph node/tumor biopsy (including FISH/Flowcytometry)	X											X
Bone marrow biopsy	X								To confirm CR[e]			X
PET /CT scan or CT scan[a]	X								After cycles 4 and 7[a]		Q6 months after Cycle 7 for 2 years. Then annually or as clinically needed afterwards.	X
Hepatitis B screen, Hepatitis C screen, and HTLV-1 serology		X										
History and physical exam including vital signs[b] and ECOG performance status			X	X			X		Monthly[f]		Q2 months for the first year, then Q4 months for second year of maintenance therapy, then Q6 months till 5 years after enrollment	X
Concomitant medications		X	X	X			X		Monthly[f]		With office visits	
Labs: CBC with differential [c], CMP [d], uric acid, LDH, phosphorous, magnesium, coagulation panel (PT/INR/PTT).			X	X	X[d]	X	X	X	X[f]	X[f]	Q2 months for the first year, then Q4 months for second year of maintenance therapy, then Q6 months till 5 years after enrollment	X
Pregnancy test for women of childbearing age (serum or urine)				X[g]								

Study Visits		Screening			Treatment Phase (1 cycle = 28 days)								Suspected PD
					Cycle 1					Cycles 2-6		Cycle 7 until 5 years	
					D1	D2	D8	D15	D22	D1	D15		Any time
Adverse events					X			X		Monthly[f]		Q2 months for the first year, then Q4 months for second year of maintenance therapy, then Q6 months till 5 years after enrollment	X
Disease assessment: Overall response assessment										After cycles 4 and 7a,e			
Study drugs	Ibrutinib 560 mg PO				• Continuous daily dosing dispensed on D1 of each cycle until disease progression or unacceptable toxicity								
	Obinutuzumab 1000 mg IV				• **Induction**: Cycle 1: Days 1, 8, and 15 will be administered. Cycles 2 to 6: Day 1 will be administered. • **Maintenance**: Patients with at least a partial response will continue to receive maintenance therapy as follows: 1000 mg of obinutuzumab to start 2 months after cycle 6 and will be given every 2 months for a total of 12 doses (2 years).								

a. Magnetic resonance imaging may be used instead of CT or PET/CT when CT with contrast or PET/CT is medically contraindicated. Imaging will be done after cycle 4 and after cycle 7. The following cycle should not be delayed while awaiting imaging results.
b. Heart rate, temperature, pulse oximeter, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position
c. Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).
d. Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST, and alkaline phosphatase. Day 2 tumor lysis labs (Potassium, Sodium, BUN, creatinine, uric acid, LDH, phosphate) for patients at high risk of TLS as assessed by the investigator.
e. A bone marrow biopsy needs to be repeated any time necessary to confirm CR by imaging except in subjects with no evidence of lymphomatous marrow involvement performed during screening (see **Error! Reference source not found.** for response criteria).
f. Physician visits and laboratory testing during Cycle 2-Cycle 6 can occur more frequently at physician discretion.
g. A negative urine or serum pregnancy test should be done within 72 hours prior to initiating protocol therapy and be practicing an effective form of contraception during protocol therapy and for at least 4 weeks following completion of protocol therapy.

** number of days prior to enrollment on the study.

Appendix 3. ECOG Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

** Oken, MM., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Available at: http://www.ecog.org/general/perf_stat.html. Accessed January 4, 2008

Appendix 4. Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to # section on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

Inhibitors of CYP3A	**Inducers of CYP3A**
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	

All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

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

Appendix 5. Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . “Transection of te oesophagus for bleeding oesophageal varices”. *The British journal of surgery*, 1973;60: 646-9.

Appendix 6. Modified Ann Arbor Staging System

Stage I: Involvement of a single lymph node region.

Stage II: Involvement of 2 or more lymph node regions on the same side of the diaphragm.

Stage III: Involvement of lymph node regions on both sides of the diaphragm.

Stage IV: Diffuse or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.

The subscript E (e.g., IIE or IIIE) is used to denote involvement of an extra lymphatic site primarily or by direct extension, rather than hematogenous spread, as in the case of a mediastinal mass extending to involve the lung.

The presence of (B) or absence of (A) fever, night sweats, and/or unexplained loss of 10% or more body weight in the 6 months prior to admission are denoted by the corresponding suffix letters B and A.

Appendix 7: Revised Criteria for Response Assessment

Response and site	PET-CT based response	CT-based response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and Extra-lymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extra nodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extra-lymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in sum of perpendicular diameters (SPD) of up to 6 target measurable nodes and extra-nodal sites. When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value.

		When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If here are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5b with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant measurable nodes and extra-nodal sites; no criteria for progressive disease are met.
Non-measured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic response**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal	Score 4 or 5b with an increase in intensity of uptake from baseline and/or	PPD progression:

masses		
Extra-nodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extra nodal site > 1.0 cm in any axis, if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to
		lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = Magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi =

shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extra nodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal

areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, and lungs), GI

involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extra nodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

[b] PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: Cheson, 2014[22]