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TITLE: A Phase Ib Study of Ibrutinib in Combination with Obinutuzumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia

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NCI-Supplied Agent(s): N/A

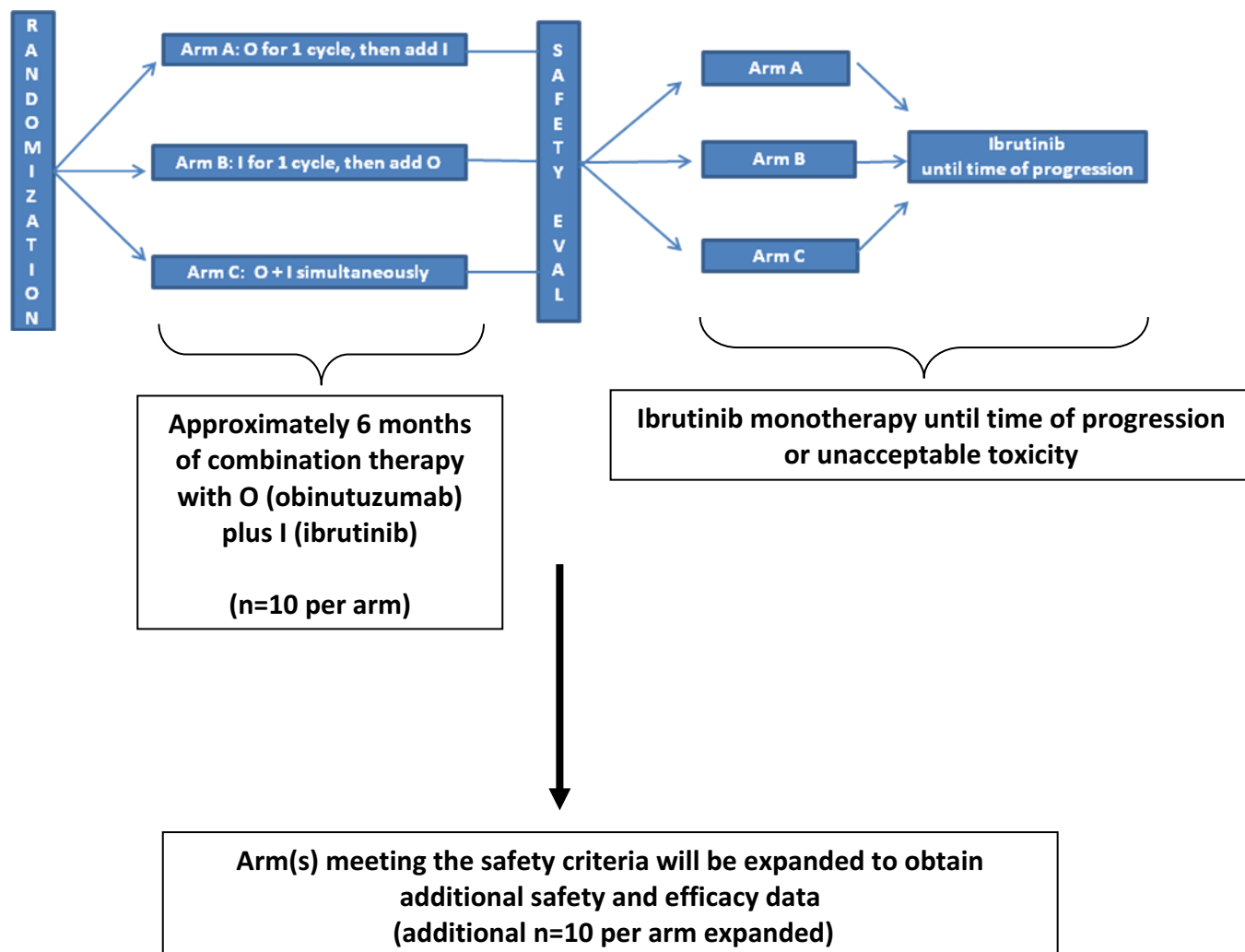
Other Agent(s): ibrutinib (commercial supply), obinutuzumab (Genentech, Inc., South San Francisco, CA)

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SCHEMA



SYNOPSIS

Study Rationale	Ibrutinib and obinutuzumab are both highly active agents that were recently FDA-approved for chronic lymphocytic leukemia (CLL). The two agents have complementary mechanisms of action and toxicity profiles, providing an initial rationale for combining them in a clinical trial. An older anti-CD20 monoclonal antibody, rituximab, was the first targeted agent to demonstrate an overall survival benefit in CLL when added to chemotherapy in a randomized, phase III study (Hallek et al., 2010). Although combinations of ibrutinib with rituximab are currently being explored in the clinic, recently it has been demonstrated <i>in vitro</i> that ibrutinib may antagonize rituximab-mediated ADCC through inhibition of the IL-2 tyrosine kinase (ITK), which is important for NK cell function (Kohrt et al., 2014). Unlike rituximab, obinutuzumab does not rely primarily on ADCC for its effector function, as it is able to potently directly kill CLL cells, likely through a lysosome-mediated process. Moreover, obinutuzumab was recently shown in a randomized, phase III study to confer an overall survival benefit when given in combination with chemotherapy to patients with CLL compared to rituximab given with the same chemotherapy (Goede et al., 2014), suggesting that obinutuzumab is a more efficacious anti-CD20 antibody in CLL. Given that these two newly-approved agents have not previously been combined, we propose a 3 arm, randomized phase Ib cohort study designed to assess the relative toxicity observed depending on how the two drugs are sequenced. At the conclusion of the phase Ib portion of the study, the approaches that meet the safety criteria will be expanded to obtain additional safety and efficacy data. <i>Rationale for exploring different sequences of administration</i> There are several viable hypotheses as to why sequence of administration with ibrutinib and obinutuzumab may be important. For example, ibrutinib causes lymphocytosis, which could increase the risk of infusion reactions to obinutuzumab but may also improve its efficacy. On the other hand, ibrutinib also mitigates the production of cytokines such as CCL3 and CCL4 which stimulate CLL cell proliferation, and therefore starting ibrutinib before obinutuzumab may actually decrease the rate of infusion reactions. Another possibility is that these effects <i>in vivo</i> are negligible and it is best to start the two drugs simultaneously for patient convenience. Our study will help determine which (if any) of these sequences of administration are better in terms of safety and efficacy, which could help define the standard of care for administration of this combination in future studies and eventually in clinical practice.
Products	Obinutuzumab is an intravenous Type II monoclonal anti-CD20 antibody, supplied by Genentech. Ibrutinib is an orally available inhibitor of Bruton's Tyrosine Kinase (BTK), commercially available in 140 mg capsules from Pharmacyclics, Inc. / Janssen Pharmaceuticals.
Study Objectives	Primary Objective To assess the safety of 3 different dosing regimens of ibrutinib plus obinutuzumab in patients with relapsed/refractory CLL

	Secondary Objectives - To assess the efficacy of ibrutinib plus obinutuzumab in patients with relapsed/refractory CLL as measured by: - Overall response rate (ORR), partial response (PR), complete response (CR) - Minimal residual disease (MRD) status in the bone marrow and blood - Duration of Response (DOR), Progression Free Survival (PFS) at 2 years, Overall Survival (OS) at 2 years - To further characterize the safety of ibrutinib plus obinutuzumab in relapsed/refractory CLL - To evaluate the association of established CLL prognostic factors including FISH cytogenetics, <i>IGHV</i> mutation status, ZAP-70, and <i>TP53</i> mutation status with clinical response Exploratory Objectives - To assess BH3 profiling as a predictive biomarker for this therapy - To assess the association of genomic markers such as <i>SF3B1</i>, <i>NOTCH1</i>, and <i>BCR/NFKB</i> pathway somatic mutation with clinical response - To evaluate for resistance mechanisms such as BTK mutation or changes in CD20 expression in patients who progress on treatment - To determine whether the rates of developing such resistance mechanisms differ depending on the sequence of therapy administration
Efficacy Endpoints	<u>Efficacy Endpoints:</u> - Overall response rate, defined as sum of CR and PR rates. Responses will be determined according to International Workshop for Chronic Lymphocytic Leukemia (IW-CLL) Response Criteria (Hallek et al. 2008 [Appendix B]) as modified by Cheson et al., 2012. - Duration of Response (DOR), 2-year Progression Free Survival (PFS), 2-year Overall Survival (OS) - Minimal residual disease (MRD) status in the bone marrow and blood
Safety Endpoints	AEs will be evaluated during the treatment period and for 30 days following discontinuation from the study using CTCAE v4.0. The DLT observation period will be the first two cycles of combination therapy.
Study Design	Subjects will be randomly assigned to each of three dose sequence arms, as follows: <i>Arm A</i> will start with 1 cycle of obinutuzumab prior to adding in daily ibrutinib in cycle 2. <i>Arm B</i> will start with daily ibrutinib for 1 cycle prior to adding in obinutuzumab in cycle 2. <i>Arm C</i> will start ibrutinib and obinutuzumab simultaneously. <i>Expansion Cohort:</i> Once 10 subjects have completed the combination portion of all three arms, a safety evaluation will be performed to determine which arms meet the safety criteria and/or the safest arm to expand. Approximately 20 eligible and evaluable patients will be accrued to the two arms that meets these criteria, to gather additional safety and efficacy data, even if the randomization results in an imbalance in the final

	number of patients in the two arms due to the stratification factors. Those that were enrolled, but never received combination therapy may be replaced in the expansion cohort.
Stratification Factors for Randomization	Age ≥ 65 or <65 , presence or absence of del(17p)
Treatment Study Visits	Each Cycle = 28 days - Patients starting with obinutuzumab (arms A and C) will have visits approximately weekly during cycle 1, bi-weekly during Cycle 2 and monthly visits in cycles 3-6. - Patients starting with ibrutinib (Arm B) will have visits on day 1 and 8 during cycle 1, approximately weekly during cycle 2, and monthly visits in cycles 3-6. - Visits will occur every 3 cycles in cycles 7-13 (Arm B will have an additional visit in Cycle 8) - After cycle 12, regular visits should occur every 3 months and efficacy assessments should occur at least every 6 months.
Baseline Lab Evaluation (Local Lab)	- CBC with differential - Comprehensive metabolic panel - Testing to rule out active Hep B, C or HIV infection - Serum pregnancy test - FISH cytogenetic analysis <i>IGHV</i>, <i>TP53</i>, and <i>NOTCH1</i> mutation status as well as ZAP-70 expression
Instrumental Tests	- Computed tomography (CT) of the chest, abdomen, pelvis (and neck if palpable cervical adenopathy is present) at screening. Disease will be assessed just prior to cycles 3, 7 (or 8 for Arm B), and 13 and then at least every 6 months (or sooner if warranted by investigator discretion). - Bone marrow biopsy is mandatory for confirmation of a complete response.
Dosing Regimen	Ibrutinib 420 mg will be administered orally once daily and given in continuous 28 day cycles. Obinutuzumab administered by IV infusion for up to 6 cycles (28-day cycles): - During first cycle: - Day 1, 100 mg obinutuzumab will be administered - Day 2, 900 mg of obinutuzumab will be administered - Days 8 and 15, 1000 mg of obinutuzumab will be administered. - During the second through sixth cycles 1000 mg of obinutuzumab will be administered on Day 1
Inclusion Criteria	Must have a confirmed diagnosis of chronic lymphocytic leukemia or small lymphocytic lymphoma as per IW-CLL 2008 criteria (Hallek et al, 2008). Specifically, patients must also require therapy for that diagnosis, based on meeting

	at least one of the following criteria: • evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin <11.0 g/L) and/or thrombocytopenia (platelets <100 x 10⁹/L) • massive (≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly • massive nodes (at least 10 cm longest diameter), progressive, or symptomatic lymphadenopathy • progressive lymphocytosis with an increase of more than 50% over a 2-month period or LDT of <6 months. • autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy • documented constitutional symptoms such as unintentional weight loss, fatigue, fevers, or night sweats Relapsed after or refractory to at least one prior CLL-directed therapy that was instituted due to patient previously meeting IWCLL 2008 criteria for treatment ECOG performance status ≤2 (see Appendix A) Patients must meet the following hematologic criteria at screening, unless they have significant bone marrow involvement of CLL confirmed on biopsy: ○ Absolute neutrophil count ≥500 cells/mm³ (0.5 x 10⁹/L). Growth factor is allowed in order to achieve this. ○ Platelet count ≥25,000 cells/mm³ (25 x 10⁹/L) independent of transfusion within 7 days of screening Adequate hepatic function defined as: Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤4.0 x upper limit of normal (ULN), bilirubin ≤2.0 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) Adequate renal function defined by serum creatinine <2.0 x ULN unless due to biopsy proven CLL kidney infiltration Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Patients who have undergone prior allogeneic transplantation are eligible provided that their transplant day 0 is > 6 months from their first dose of study drug Ability to understand and the willingness to sign a written informed consent document
Exclusion Criteria	Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) within 2 weeks of Cycle 1/Day 1 with the following exceptions: ○ Corticosteroid therapy (prednisone or equivalent ≤20 mg daily) is allowed as clinically warranted as long as the dose is stabilized at least for 7 days prior to initial dosing. Topical or inhaled corticosteroids are permitted. ○ Patients who may experience clinical deterioration may start

	therapy after a shorter washout period with prior approval by the PI Allogeneic hematologic stem cell transplant within 12 months. Post allo patients must not have active graft versus-host disease and be off all immune suppression (other than steroids, as above). History of severe allergic or anaphylactic reactions to monoclonal antibody therapy Prior treatment with either obinutuzumab or ibrutinib History of other malignancies, except: ○ Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician. ○ Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. ○ Adequately treated carcinoma in situ without evidence of disease. ○ Low-risk prostate cancer on active surveillance Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone) within 28 days of the first dose of study drug. Vaccinated with live, attenuated vaccines <4 weeks before first dose of study drug. Recent infection requiring systemic treatment that was completed ≤ 7 days before the first dose of study drug. Known bleeding disorders (eg, von Willebrand's disease) or hemophilia. History of stroke or intracranial hemorrhage within 6 months prior to enrollment. Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or hepatitis B virus (HBV). Any uncontrolled active systemic infection. Major surgery within 4 weeks of first dose of study drug. 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. 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 randomization. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. Lactating or pregnant. Patients receiving any other study agents Patients with known CNS involvement Baseline QTcF >480 ms. NOTE: This criterion does not apply to patients with a left bundle branch block. Patients who require warfarin or other vitamin K antagonists for anticoagulation
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	(other anticoagulants are allowed after consultation with the Principal Investigator). Concurrent administration of medications or foods that are strong inhibitors or inducers of CYP3A Patients with ongoing use of prophylactic antibiotics are eligible as long as there is no evidence of active infection and the antibiotic is not included on the list of prohibited medications Significant co-morbid condition or disease which in the judgment of the PI would place the patient at undue risk or interfere with the study
Sample Size	Estimated to be between 40 and 60 (10 patients in each of the 3 arms and then approximately 10 eligible and evaluable patients in each arm that is expanded)

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1. OBJECTIVES

1.1 Study Design

This is a phase Ib study of the oral BTK inhibitor ibrutinib in combination with the type II, glycoengineered anti-CD20 monoclonal antibody obinutuzumab in patients with relapsed or refractory chronic lymphocytic leukemia. The study includes 3 different cohorts of 10 patients each: *Cohort A* will start with 1 cycle (4 weeks) of obinutuzumab prior to adding in daily ibrutinib in cycle 2. *Cohort B* will start with daily ibrutinib for 1 cycle (4 weeks) prior to adding in obinutuzumab. *Cohort C* will start ibrutinib and obinutuzumab simultaneously. Each arm that meets the safety criteria will be chosen to move on to an expansion cohort of approximately 10 patients to further evaluate the safety and preliminary efficacy of the combination. There is no control group on this study, and patients will be randomized to each cohort. A total of 20 eligible and evaluable patients will be accrued and randomized between the two arms that meet these criteria to gather additional safety and efficacy data. Patients who were enrolled but never received combination therapy may be replaced in the expansion cohort.

1.2 Primary Objectives

- To assess the safety of 3 different dosing regimens of ibrutinib plus obinutuzumab in patients with relapsed or refractory CLL

1.3 Secondary Objectives

- To assess the efficacy of ibrutinib plus obinutuzumab in patients with relapsed/refractory CLL as measured by:
 - Overall response rate (ORR), partial response (PR), complete response (CR)
 - Minimal residual disease (MRD) status in the bone marrow and blood
 - Duration of Response (DOR), 2-year Progression Free Survival (PFS), 2-year Overall Survival (OS)
- To further characterize the safety of ibrutinib plus obinutuzumab in relapsed/refractory CLL
- To evaluate the association of established CLL prognostic factors such as FISH cytogenetics, *IGHV* mutation status, ZAP-70, and *TP53* mutation status with clinical response

1.4 Exploratory Objectives

- To assess BH3 profiling as a predictive biomarker for this therapy
- To assess the association of genomic markers such as *SF3B1*, *NOTCH1*, and *BCR/NFKB* pathway somatic mutation with clinical response
- To evaluate for resistance mechanisms such as BTK mutation or changes in CD20 expression in patients who progress on treatment
- To determine whether the rates of developing such resistance mechanisms differ depending on the sequence of therapy administration

2. BACKGROUND

2.1 Study Disease(s)

Overview

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western hemisphere, with about 16,000 new cases per year diagnosed in the U.S. alone. Despite recent advances in treatment options, the disease remains incurable by conventional therapies. This disease was initially treated with alkylating agents like chlorambucil, and increased complete remission rates and progression-free survival were later observed with the nucleoside analogue, fludarabine (Rai, et al., 2000). Fludarabine-based combinations were then developed, demonstrating superior complete remission rates and progression-free survival (PFS) with the addition of either cyclophosphamide and/or rituximab to fludarabine alone (O'Brien et al., 2001 and Byrd et al., 2005). More recently, an overall survival benefit has been demonstrated by the inclusion of rituximab with fludarabine and cyclophosphamide (FCR) over fludarabine and cyclophosphamide alone (FC) in patients with previously untreated CLL (Hallek et al., 2010).

Limitations of Current Therapy

Despite these encouraging improvements over the years, patients inevitably relapse after chemoimmunotherapy, and the disease remains incurable by conventional therapy. Salvage chemotherapy regimens typically have lower response rates, and even those who respond have shorter PFS than after initial therapy. Moreover, chemotherapy for relapsed or refractory patients typically has more toxicity than when it is given in the frontline setting. All of these factors have prompted intensive investigation over the last several years into developing novel, targeted agents with improved efficacy and decreased toxicity compared to chemotherapy.

B Cell Receptor Pathway

The B cell receptor (BCR) pathway is now firmly established as an important target for the treatment of CLL (reviewed in Davids et al., 2012). Although not activated by somatic mutation, nonetheless the BCR pathway is constitutively active in CLL and further inducibly activated within microenvironmental niches. Indeed, upregulation of the BCR pathway is now thought to be a hallmark of the pathophysiology underlying chronic lymphocytic leukemia (CLL).

Bruton's Tyrosine Kinase

A key protein in the BCR pathway is Bruton's tyrosine kinase (BTK). The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite 2000). In vitro inhibition of BTK results in abrogation of survival signaling downstream of the BCR, a decrease in pro-survival cytokines, and modest induction of CLL cell

apoptosis (Herman, et al., 2011). Moreover, inhibition of BTK in CLL cells in vitro with siRNA promotes apoptosis, and BTK inhibition in the TCL1 mouse model of CLL significantly delays the development of CLL, suggesting that BTK is a critical kinase for CLL development and expansion (Woyach et al., 2013).

The Limitations of Ibrutinib Monotherapy

Ibrutinib was approved for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL) in 2014, based on a high level of efficacy and an excellent safety profile, as detailed in section 2.2.3.2. Although ibrutinib monotherapy is an effective therapy for relapsed or refractory CLL, not all patients respond to ibrutinib therapy, and even in patients who do respond, resistance mechanisms have already arisen, such as the C481S binding site mutations recently described in CLL (Woyach et al, 2014). Notably, while 71% of CLL patients achieved an objective response to single agent ibrutinib in the initial phase Ib/II study, only 2% of patients achieved a CR, with the remainder of patients achieving a PR. Additionally, patients with high risk cytogenetics (deletion 17p) displayed a shorter progression free survival compared to those patients with favorable prognostic markers (median about 28 months vs. not reached) (Byrd et al., 2013). Moreover, in the phase III, randomized study of ibrutinib vs. ofatumumab (RESONATE), the response rate for ibrutinib was only 42.6% by IW-CLL criteria, although including the patients with PR with lymphocytosis the true response rate was 62.6% (Byrd et al., 2014). Though promising, these studies of ibrutinib suggest that there is an urgent need to develop a combination partner for ibrutinib that could increase the complete response rate and lengthen the duration of response, particularly for high risk patients.

Anti-CD20 Therapy in CLL

One logical combination partner for ibrutinib is a monoclonal antibody, due to non-overlapping toxicity and potential for synergy. The first monoclonal anti-CD20 antibody to be utilized for the treatment of CLL was rituximab, a type 1 chimeric antibody. The addition of rituximab to chemotherapy increased the response rate, progression free, and overall survival in a randomized, phase III study, the German CLL 8 study (Hallek et al., 2010). Recently, the combination of ibrutinib with rituximab was found to be safe and well-tolerated (Burger et al., 2014).

In 2009, a second anti-CD20 antibody, ofatumumab, was FDA-approved for the treatment of relapsed/refractory CLL. Ofatumumab is a fully humanized, type I monoclonal antibody that binds to a distinct small-loop epitope on the CD20 molecule, leading to enhanced complement-dependent cytotoxicity compared to rituximab (Teeling et al., 2006). In a study of patients with highly refractory CLL, ofatumumab monotherapy led to about a 50% overall response rate, with a median PFS of about 6 months (Wierda et al., 2010).

As detailed in section 2.2.4, obinutuzumab is a type II, glycoengineered, fully humanized anti-CD20 monoclonal antibody with the ability to induce potent antibody dependent cellular cytotoxicity as

well as directly inducing CLL cell death. Obinutuzumab was FDA approved in combination with chlorambucil for the initial therapy of CLL in 2014 (Goede et al., 2014).

2.2 IND Agent(s)

2.2.1 *Ibrutinib*

Ibrutinib (formerly PCI-32765) is a first-in-class potent, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently under development for the treatment of B-cell malignancies. Ibrutinib is being co-developed by Pharmacyclics, Inc. and Janssen Research & Development, LLC (JRD) as IMBRUVICA™, and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with CLL and mantle cell lymphoma who have received at least one prior therapy. The drug is also currently under investigation in various other B cell malignancies. "PCI-32765" and "ibrutinib" refer to the same molecule; hereafter, "ibrutinib" will be used. The investigational drug product is an oral formulation in a hard gelatin capsule form containing micronized ibrutinib.

Data from the phase I dose finding study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥ 2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration. For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure.

2.2.2 Nonclinical Studies

2.2.2.1 Pharmacology

In vitro studies have shown that ibrutinib binds covalently to a cysteine residue 481 near the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity. In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited autophosphorylation of BTK, and phosphorylation of further downstream kinases. Ibrutinib was designed as a selective and covalent inhibitor of the Btk (Pan et al., 2007). In vitro, ibrutinib is a potent inhibitor of Btk activity ($IC_{50} = 0.39$ nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation ($IC_{50} = 80$ nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011)

Ibrutinib arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models (Herman 2011) Ibrutinib also inhibited adhesion and migration of mantle cell lymphoma (MCL) cells in co-culture and reduced tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression (Chang 2013a, Chang 2013b)

2.2.2.2 Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

2.2.2.3 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib. Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg. Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively.

2.2.3 Clinical Studies

2.2.3.1 Human Pharmacokinetics

Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with chronic lymphocytic leukemia (CLL) approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of Btk, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male

subjects demonstrated that less than 10% of the total dose of [¹⁴C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance > 30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in patients with severe renal impairment or patients on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

Data from Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥ 2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

2.2.3.2 Clinical Efficacy Studies in CLL/SLL

Subjects with CLL or SLL have received single-agent ibrutinib in several published clinical studies. The first studies to include CLL patients were: Study PCYC-04753, a Phase 1 dose-escalation study in subjects with recurrent B-cell lymphoma, and Study PCYC-1102-CA, a Phase 1b/2 study in subjects with treatment-naïve or relapsed/refractory CLL/SLL (Byrd, et al., 2013 and O'Brien et al., 2014).

Study PCYC-04753

Study PCYC-04753 was a multicenter Phase 1 dose-finding study in subjects with relapsed or refractory B-cell Non-Hodgkin Lymphoma (NHL), including CLL, and Waldenström's macroglobulinemia. In the 50 evaluable patients, the overall response rate (ORR) was 60%, including a complete response (CR) rate of 16%. The median PFS was 13.6 months. The most promising efficacy signal in this study was in CLL/SLL (11 of 16 patients responded (two CRs) (Advani et al., 2013).

Study PCYC-1102-CA

Study PCYC-1102-CA is a Phase 1b/2, open-label, multicenter study in subjects with treatment naïve or relapsed/refractory CLL/SLL.

Relapsed/Refractory Cohort

Eighty-five patients with relapsed or refractory CLL/SLL were enrolled and received either 420 mg (n=51) or 840 mg (n=34) daily on a continuous schedule until time of progression or unacceptable toxicity (Byrd et al., 2013). The majority of patients on this study were considered to have high-risk disease based on CLL/SLL prognostic markers and/or short response to prior therapies. The overall response rate based on standard IW-CLL criteria was 71% (including 2 CRs). As with other inhibitors of the BCR pathway, the drug caused redistribution lymphocytosis in the majority of patients, and therefore an additional 15 patients had a nodal response with lymphocytosis, meaning that about 88% of patients achieved clinical benefit from the drug. The response rate did not vary according to most of the traditional high-risk prognostic features such as del(17p), where the overall response rate was 68%. Interestingly, patients with unmutated IGHV actually had a higher response rate of 77% compared to mutated IGHV

patients ($p=0.005$), likely due to the fact that the lymphocytosis resolved more quickly in the unmutated group. These promising responses have proven to be durable for the majority of patients, with a 26 month estimated rate of PFS of 75%.

RESONATE Study

The promising results of the phase Ib/II study were confirmed in the randomized, phase III RESONATE study that demonstrated both a PFS and OS benefit of ibrutinib over a CD20 monoclonal antibody ofatumumab in relapsed/refractory CLL (Byrd et al., 2014).

Ibrutinib FDA Approval

These studies led to ibrutinib (IMBRUVICA™) receiving full approval by the U.S. Food and Drug Administration (FDA) in July 2014 for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy or have del(17p).

Combination Studies of Ibrutinib for CLL

Although the efficacy data for ibrutinib as a single agent in CLL are strong, there have been few complete remissions, and at least based on the currently available data, it seems unlikely that the drug has curative potential as a single agent. Therefore, much attention has recently been focused on finding optimal combination partners for ibrutinib to improve the depth and duration of response and perhaps even to devise a curative combination treatment strategy.

Ibrutinib plus Antibody

Given that monoclonal anti-CD20 antibodies are typically well-tolerated and active in combination with other therapies in CLL, it is not surprising that the first combination studies with ibrutinib in CLL were with these agents. A phase 2 study of ibrutinib plus rituximab enrolled 40 patients who were treated with continuous ibrutinib at 420 mg daily along with weekly rituximab (375 mg/m^2) for 4 weeks, then monthly until cycle 6, at which point responders continued on ibrutinib alone until progression (Burger et al., 2014). The median age was 65, with a median of 2 prior therapies. Half of the patients had either del(17p) or *TP53* mutation, and 80% of patients had unmutated *IGHV*. The ORR was 95%, including 8% CR, with one of the CR patients achieving minimal residual disease (MRD) negativity by flow cytometry. The 20 patients with del(17p) or *TP53* mutation had a response rate of 90%, with 2 patients achieving CR. Quality of life was also measured in this study and was found to improve significantly over the course of the study. As expected, lymphocyte redistribution resolved more rapidly and completely compared to patients in prior studies of ibrutinib monotherapy.

Promising results have also been reported with the combination of ibrutinib with the fully-humanized anti-CD20 monoclonal antibody ofatumumab. A phase 1b/2 study in relapsed/refractory CLL is evaluating 3 different dosing schedules of the ibrutinib ofatumumab combination, and data have been presented on the schedule that starts ibrutinib 4 weeks prior to starting ofatumumab, which is then given for a standard 6 month course, with ibrutinib continued as maintenance at the conclusion of the combination portion of the study (Jaglowksi et al., 2012). Twenty-seven patients have been reported thus far, with a median age of 66 years and median of 3 prior therapies. This was a high risk group, with 37% having del(17p), 33% having del(11q), and 91% having unmutated *IGHV*. All 27 patients achieved a response by IW-CLL criteria,

including 1 patient with a CR. At a median 9.8 months of follow-up, 89% of patients remained on study, with only 1 patient coming off study for progressive disease. Interestingly, this study included 3 patients with Richter's syndrome, and 2 of the 3 achieved a response, with one Richter's patient remaining on study in ongoing response at 10.1 months.

The strong efficacy data along with the favorable toxicity profile of these early studies of ibrutinib with monoclonal antibodies are promising, and support the development of larger randomized studies of this strategy.

Summary of Efficacy of Ibrutinib in CLL

Efficacy results from studies of ibrutinib as both a single agent and in combination with chemotherapy and monoclonal antibodies show that the drug has robust activity in CLL. The studies included subjects with previously treated CLL, as will be the population in this trial. Response rates for the studies were independent of risk factors including age or poor prognostic features, including del(17p) positivity. The predictable and characteristic pattern of response, with rapid reduction in lymphadenopathy, frequent and early hematologic improvement, and transient lymphocytosis, is consistent with the established anti-homing, anti-adhesion, pro-apoptotic, and anti-proliferative effects of BTK inhibition in CLL cells.

2.2.3.3.1 Drug-Drug Interaction

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4/5. Guidelines for the use of CYP3A inhibitors or inducers is outlined below.

Agents That May Increase Ibrutinib Plasma Concentrations (CYP3A4/5 Inhibitors)

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and AUC_{0-last} , of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤ 2 -fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, consider reducing ibrutinib dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Appendix B).

Agents That May Decrease ibrutinib Plasma Concentrations (CYP3A4/5 Inducers)

Co-administration of ibrutinib with strong CYP3A inducers, rifampin, in healthy subjects decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

An abbreviated list of inhibitors, inducers, and substrates is in Appendix B, and a more comprehensive list may be found at <http://medicine.iupui.edu/clinpharm/ddis/main-table/>. This website is continually revised and should be checked frequently for updates.

QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with ECGs and electrolytes should be considered and if needed, the principal investigator should be contacted.

Other Malignancies

In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

2.2.4 Obinutuzumab

2.2.4.1 Structure and Mechanism of Action of Obinutuzumab

Obinutuzumab (GA101, RO5072759), is a glycoengineered, humanized, type II anti-CD20 monoclonal antibody (mAb). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics (Beers et al. 2010; Mössner et al. 2010): 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 FcγRIII positive immune effector cells such as natural killer (NK) cells, macrophages and monocytes; and high direct cell death induction.

2.2.4.2 Tolerability and Efficacy of Obinutuzumab in Chronic Lymphocytic Leukemia

Study BO20999 (GAUGUIN; NCT00517530) (Phase I)

BO20999 was an open-label, multicenter, Phase I/II study to explore obinutuzumab safety and activity in relapsed/refractory NHL and CLL. Thirteen CLL patients have received obinutuzumab at doses with a range of 400–2000 mg (given as a flat dose) across four cohorts (Morschhauser et al. 2009). There were no dose-limiting toxicities (DLTs) and no requirement for dose reductions. Infusion-related reactions (IRRs) occurred in all CLL patients and were characterized predominantly by National Cancer Institute Common Terminology Criteria (NCI-CTC) Grade 1–2 toxicities: chills, nausea, vomiting, fever, pyrexia, hypertension, hypotension, dyspnea, and dizziness. Two patients experienced four NCI-CTC Grade 3 toxicities: sweats, flushing, asthenia, and hepatic cytolysis.

Although the safety profile appears otherwise similar between NHL and CLL, there was an increase in NCI-CTC v3.0 Grade 3/4 neutropenia noted in CLL patients, which were observed in 9 patients across the four dose levels administered. Five patients experienced NCI-CTC Grade 4 neutropenia and 4 patients experienced NCI-CTC Grade 3 neutropenia as the maximum severity.

Of the 9 patients, 7 had one NCI-CTC Grade 3/4 event and 2 patients experienced more than one event. Granulocyte colony-stimulating factor (G-CSF) support was administered to 6 of the 9 patients, and these patients responded quickly to G-CSF support. For the 3 patients who did not receive G-CSF, neutrophil counts normalized spontaneously. Furthermore, it is important to note that these neutropenia events did not appear to be accompanied by a higher incidence of infections. No deaths were reported in Phase I of this study for CLL.

As assessed by the International Workshop on CLL (IWCLL) criteria, the end-of-treatment response rate with obinutuzumab monotherapy was 62% (8 of 13 patients with partial response [PR]) (Morschhauser et al. 2009).

Study BO20999 (GAUGUIN; NCT00517530) (Phase II)

Twenty patients with *relapsed/refractory* CLL have received 1000 mg of obinutuzumab. The most commonly reported adverse event (AE) during the treatment period was IRR, reported in 19 (95%) of 20 patients. Fifteen patients experienced Grade 3/4 AEs of whom 14 patients had treatment-related Grade 3/4 AEs (investigator assessment). Treatment-related Grade 3/4 AEs were IRR (6 patients), neutropenia (4 patients), lymphopenia (2 patients), thrombocytopenia (2 patients), and anemia, pure red cell aplasia, pancytopenia, febrile neutropenia, herpes zoster, and interstitial lung disease (1 patient each). Eleven serious adverse events (SAEs) in 9 patients were reported during treatment, 9 of which were assessed by the investigator as related to obinutuzumab: IRR (4 patients) and febrile neutropenia, pancytopenia, pure red cell aplasia, interstitial lung disease and pyrexia (1 patient each). Three patients withdrew from further study treatment after the first infusion due to IRR. One death has been reported during follow-up from colon cancer. The most common AE in follow-up was nasopharyngitis, reported in 2 patients. End-of-treatment response assessment showed that four patients (20%) achieved a clinical response, with a best overall response rate (ORR) of 25% in evaluable patients (Salles et al. 2011).

Study BO21003 (GAUSS; NCT00576758) (Phase I)

BO21003 is an open-label, dose-escalating, multicenter Phase I/randomized Phase II study in patients with relapsed/refractory CD20+ malignant disease. In Study BO21003, 5 CLL patients have been administered obinutuzumab. The fifth patient withdrew at Cycle 1, Day 1 because of a Grade 4 IRR, which occurred minutes after the start of infusion in the setting of high tumor burden. Efficacy assessments are available for only the 4 patients who completed treatment (received 4 cycles of infusion). The end-of-treatment response in patients with CLL receiving obinutuzumab monotherapy in this study included 3 stable disease and 1 progressive disease patients (Sehn et al. 2009).

Study GAO4768g / GAGE / NCT01414205 (Phase II)

GAO4768g is an open-label, randomized, multicenter, Phase II study evaluating the efficacy and safety of obinutuzumab administered at 1000 mg versus 2000 mg doses in patient with previously untreated CLL. The results of the GAGE study were presented at the 2014 ASCO meeting. Eighty patients were randomized and stratified based on Rai stage and tumor mass.

For patients who received the 1000-mg doses, obinutuzumab was administered with three 1000-mg doses in the first 21-day cycle (the first 1000-mg dose was administered over 2 days: 100 mg

administered on Day 1, 900 mg administered on Day 2; 1000 mg was administered on both Days 8 and 15). In the subsequent cycles (2 – 8), 1000 mg of obinutuzumab was administered on the first day of each cycle.

For patients who received the 2000-mg doses, obinutuzumab was administered as follows: 100 mg on Cycle 1, Day 1; 900 mg on Day 2; and 1000 mg on Day 3. On Days 8 and 15 of Cycle 1, 2000 mg was administered on each day. For Cycles 2 – 8, 2000 mg of obinutuzumab was administered on Day 1 of each cycle.

ORR was assessed at 2 months post-therapy according to the IWCLL criteria. The ORR for the 1000 mg and 2000 mg obinutuzumab treatment arms were 49% compared with 67%, respectively; 2-sided $p = 0.0779$. Complete response/complete remission with incomplete blood count recovery (CR/CRi) were achieved by 5% of patients (2/41) in the 1000-mg arm compared with 21% of patients (8/39) in the 2000-mg arm. The most common Grade 3/4 AEs were IRRs (23% vs. 11%) and neutropenia (3% vs. 5%) for the 1000-mg and 2000-mg arms, respectively (Flynn et al. 2014).

Study GAO4779g (GALTON; NCT01300247) (Phase II)

GAO4779g is an open-label, non-randomized, multicenter, Phase II study. In the GALTON study, 41 patients with untreated CLL were treated with obinutuzumab 1000 mg (100 mg IV on Day 1, 900 mg on Day 2, and 1000 mg on Days 8 and 15 of Cycle 1; 1000 mg on Day 1 in Cycles 2 – 8) and FC or B given at standard dosing. Each cycle was 28 days long.

The most common AEs (any grade) occurring in the G-FC arm were obinutuzumab-related IRRs (91%), nausea (76%), fatigue (57%), constipation (48%), and neutropenia (43%); in the G-B arm, they were obinutuzumab-related IRRs (90%), nausea (65%), neutropenia (55%), diarrhea (50%), and pyrexia (45%). The most common Grade 3/4 AEs were obinutuzumab-related IRRs (29%, 10%), neutropenia (43%, 55%), and infections (19%, 5%) for G-FC and G-B, respectively.

Fourteen patients experienced SAEs (G-FC, $n = 6$; G-B, $n = 8$), with events including febrile neutropenia (5 events); infections (4 events); IRRs (3 events); nausea, vomiting, pyrexia (2 events each); and diarrhea, fatigue, tachycardia, tumor lysis syndrome, syncope, mental status changes, neutropenia, face swelling, and hypertension (1 event each). Nine patients (G-FC, $n = 7$; G-B, $n = 2$) had AEs leading to treatment discontinuation, including Grade 3/4 neutropenia (3 patients in G-FC [1 of these 3 patients also had Grade 4 cellulitis] and 2 patients in G-B), Grade 3 thrombocytopenia (2 patients in G-FC), Grade 4 pancytopenia (1 patient in G-FC), and Grade 4 aspartate aminotransferase (AST)/Grade 3 alanine aminotransferase (ALT) elevation (1 patient in G-FC).

The ORR was 62% (CR, 2; CRi, 3; PR, 8) in patients who received G-FC and 90% (CR, 4; CRi, 5; PR, 9) in patients who received G-B, including 6 patients (G-FC, $n = 4$; G-B, $n = 2$) not evaluable due to inadequate response evaluation. Four patients in the G-FC arm (0 in G-B) had stable disease during and after therapy. No patient progressed during the study (Brown et al. 2013).

Study BO21004 (CLL11; NCT01010061) (Phase III)

This is an ongoing, open-label, multicenter, three-arm randomized, Phase III study to compare the efficacy and safety of obinutuzumab + chlorambucil (GClb), rituximab + GClb (RClb), or Clb alone in previously untreated CLL patients with comorbidities. BO21004 enrolled 781 patients and an additional 6 patients during a safety run-in period before randomization. An analysis based on data collected by the data cutoff date for these 6 patients accrued from December 2009 until February 2010 for the BO21004 safety run-in phase showed that all 6 patients completed 6 cycles of treatment but two patients had significant dosing delays. IRRs occurred in 5 patients, all were Grade 1 or 2, with no severe IRRs. All 6 patients experienced neutropenia, 5/6 patients reported Grade 3 – 4 afebrile neutropenia with no febrile neutropenia. All 6 reported thrombocytopenia with one case of Grade 3 – 4 thrombocytopenia. No patient died during the safety run-in period. Given that none of the pre-defined stopping criteria were met during this safety run-in period, Study BO21004 opened to randomization in April 2010 (Goede 2012).

Study BO21004 includes two separate stages evaluating efficacy and the primary endpoint is progression-free survival (PFS). Stage 1 evaluated obinutuzumab + chlorambucil compared with chlorambucil alone.

In the Stage 1 analysis, the safety and efficacy of obinutuzumab + chlorambucil or rituximab + chlorambucil was compared with chlorambucil alone. Compared with chlorambucil, both obinutuzumab + chlorambucil and rituximab + chlorambucil demonstrated statistically significant PFS benefit compared with chlorambucil alone. Median PFS of chlorambucil vs. obinutuzumab + chlorambucil was 11.1 vs. 23 months, respectively, (median observation time, 14.2 months; hazard ratio [HR], 0.16 [0.11 – 0.24]; $p < 0.0001$; stratified log-rank test) as assessed by independent review.

In the Stage 2 analysis of this study, obinutuzumab + chlorambucil was compared with rituximab + chlorambucil. At the pre-planned interim analysis, the primary endpoint was met early and the results were released by the independent data monitoring board. Median PFS was 26.7 months vs. 15.2 months for obinutuzumab + chlorambucil vs. rituximab + chlorambucil, respectively. The ORR was 78% vs. 65%, and CR was 21% vs. 7%, respectively. (Goede et al. 2014; Obinutuzumab USPI).

For more information related to safety and efficacy in the CLL indication, please refer to the Obinutuzumab Investigator's Brochure or the *Obinutuzumab USPI*.

2.2.4.3 Additional Overview of Safety of Obinutuzumab

Obinutuzumab has been administered to greater than 1,310 patients with CD20-positive malignancies. Both in patients with NHL and with CLL, IRR was the most common AE in clinical trials conducted to date. They were predominantly associated with the first infusion, generally occurring early during the infusion, shortly after, or in some cases up to 24 hours after the completion of the infusion with obinutuzumab. The incidence and intensity of IRRs decreased with subsequent infusions of obinutuzumab. In a few patients, concurrent signs of tumor lysis syndrome (TLS) were observed. Other frequently observed AEs include infections

and neutropenia. These events appeared to be more common in patients with CLL compared to NHL.

In trials investigating the combination of obinutuzumab and CHOP, FC, chlorambucil or bendamustine, the incidence of AEs in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. So far, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of AEs have been determined.

A pooled analysis of safety data for obinutuzumab collected during the monotherapy studies BO20999 and BO21003 was conducted in patients with NHL (aggressive [aNHL] and indolent [iNHL]) or CLL who participated in those two studies (both Phase I and Phase II) and received monotherapy treatment with obinutuzumab and included a total 205 patients with NHL (49 aNHL and 156 iNHL patients) and 38 patients with CLL.

In the group of 38 patients with CLL treated with obinutuzumab monotherapy, the majority of patients (25 [66%]) were treated for ≥ 4 weeks to < 6 months. Eleven patients (29%) were exposed for 6 to < 12 months, and two patients (5%) were exposed for 12 months or longer. Eight of 38 patients (21%) with CLL were withdrawn during the treatment phase; 4 patients (11%) were withdrawn due to AEs, which indicates that AEs were mostly manageable. Almost all patients (37/38 [97%]) experienced an IRR. The number of patients with Grade 3/4 IRRs was 11/38 (29%). As is typical for patients with CLL, blood and lymphatic system disorders were among the most frequently reported AEs, in particular neutropenia (13/38 patients [34%]), febrile neutropenia (5/38 patients [13%]), and thrombocytopenia (7/38 patients [18%]). Infections and infestations were common AEs, occurring in 21/38 patients (55%). Infections reported in more than one patient were nasopharyngitis (6 patients), bronchitis and sinusitis (4 patients each), influenza and lung infection (3 patients each), and herpes zoster and oral herpes (2 patients each).

Thirteen patients (34%) died, 8 of these due to disease progression. One patient died from an unspecified cause after withdrawal from the study for lack of response. This patient had received subsequent experimental therapies and had stable CLL at the time she died. For 4 additional patients, the cause of death was reported as colon cancer, lung adenocarcinoma, metastasis, and septic shock, and all were considered not to be related to treatment.

In the two studies investigating obinutuzumab as monotherapy, BO20999 and BO21003, patients with CLL appeared to be at a higher risk of experiencing an AE of special interest than patients with NHL. The largest difference in the incidences was seen for neutropenia (occurring in 47% of patients with CLL [18/38] vs. 8% of patients with aNHL [4/49] and 8% of patients with iNHL [13/156]) and treatment-related AEs associated with the infusion (100% [38/38] vs. 80% [39/49] and 83% [129/156]).

To date, a very small number of patients have experienced TLS (six in total); four patients in the aNHL population (population including MCL) and one patient each in the CLL and iNHL populations.

Infections have been reported in 21/38 CLL patients (55%). One CLL patient and one iNHL patient died from an infection (septic shock in both cases) during survival follow-up 671 days and 494 days after last dose of treatment, respectively. Three CLL patients were withdrawn from treatment due to an AE of special interest, all for IRRs.

In the Phase III Study BO21004 (CLL11), comparison of obinutuzumab + chlorambucil to chlorambucil alone showed that the most common AEs (all grades, Grades 3 – 4), respectively, were IRRs (69% vs. 0, 21% vs. 0), neutropenia (40% vs. 18%, 34% vs. 16%), thrombocytopenia (15% vs. 7%, 11% vs. 3%), anemia (12% vs. 10%, 4% vs. 5%), leukopenia (7% vs. 0, 5% vs. 0), pyrexia (10% vs. 7%, < 1 vs. 0), and cough (10% vs. 7%, 0 vs. < 1%).

The incidence of IRRs was 69% with the first infusion of obinutuzumab. The incidence of Grade 3 or 4 IRRs was 21%, with 8% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3%, with the second 1000-mg dose and <1% thereafter. No Grade 3 or 4 IRRs were reported beyond the first 1000- mg infusion. Of the first 53 patients receiving obinutuzumab in the trial, 47 (89%) experienced an IRR. After this occurrence, study protocol modifications were made to require pre-medication with a corticosteroid, antihistamine, and acetaminophen. The first dose was also divided into two infusions (100 mg on Day 1 and 900 mg on Day 2). Of the 45 patients for whom these mitigation measures were implemented, 21 patients (47%) experienced a reaction with the first 1000-mg dose and <2% thereafter. The incidence of neutropenia reported as an AE was 40% in the obinutuzumab-treated arm and 18% in the chlorambucil-alone arm, with the incidence of SAEs being 1% and 0%, respectively. Cases of late-onset neutropenia (occurring 28 days after completion of treatment or later) were 16% in the obinutuzumab-treated arm and 12% in the chlorambucil-alone arm.

The incidence of infections was similar between arms. Thirty-eight percent of patients in the obinutuzumab- treated arm experienced an infection, 9% were Grade 3 – 4, and none were fatal. The incidence of thrombocytopenia reported as an AE was 15% in the obinutuzumab-treated arm and 7% in the chlorambucil-alone arm. Five percent of patients in the obinutuzumab-treated arm experienced acute thrombocytopenia (occurring within 24 hours after the obinutuzumab infusion).

The incidence of Grade 3 or 4 tumor lysis syndrome was 2% in the obinutuzumab-treated arm vs. 0% in the chlorambucil-alone arm. AEs related to musculoskeletal disorders, including pain (System Organ Class), have been reported with obinutuzumab with higher incidence than with the comparator (17% vs. 13%, respectively) (Goede et al. 2013).

Obinutuzumab FDA approval

Based on the data above including the positive results of the randomized phase III BO21004 (CLL11) study, obinutuzumab received FDA approval in late 2013 for use in combination with chlorambucil in previously untreated patients with CLL.

2.3 Rationale

Rationale for the combination

Ibrutinib and obinutuzumab are both highly active agents that were recently FDA-approved for relapsed or refractory CLL. The two agents have complementary mechanisms of action and toxicity profiles, providing an initial rationale for combining them in a clinical trial. An older anti-CD20 monoclonal antibody, rituximab, was the first targeted agent to demonstrate an overall survival benefit in CLL when added to chemotherapy in a randomized, phase III study (Hallek et al., 2010). Although combinations of ibrutinib with rituximab are currently being explored in the clinic, recently it has been demonstrated *in vitro* that ibrutinib may antagonize rituximab-mediated ADCC through inhibition of the IL-2 tyrosine kinase (ITK), which is important for NK cell function (Kohrt et al., 2014). Unlike rituximab, obinutuzumab does not rely primarily on ADCC for its effector function, as it is able to potently directly kill CLL cells, likely through a lysosome-mediated process. It also has enhanced capacity for ADCC based on its Type II, glycoengineered structure. A recent study found that the inhibitory effect of ibrutinib on the immune effector mediated activity obinutuzumab is not observed when compared to rituximab (Herter et al., 2014). ADCC at saturating antibody doses, whole blood B cell depletion and *in vivo* efficacy of obinutuzumab were retained in presence of clinically relevant concentrations of ibrutinib covering C_{max} and C_{trough} levels, whereas the activity of rituximab was almost completely abolished under these conditions. The superiority of obinutuzumab over rituximab in CLL was also recently shown in a randomized, phase III study, where obinutuzumab conferred an overall survival benefit when given in combination with chemotherapy compared to rituximab given with the same chemotherapy (Goede et al., 2014), suggesting that obinutuzumab is a more efficacious anti-CD20 antibody in CLL.

Given that these two newly-approved agents have not previously been combined, we propose a 3 arm phase Ib cohort study designed to assess the relative toxicity observed depending on how the two drugs are sequenced. At the conclusion of the phase Ib portion of the study, the approaches that meet the safety criteria will be expanded to obtain additional safety and efficacy data.

Rationale for exploring different sequences of administration

The sequence of administration of CD20 antibodies and ibrutinib may have a significant influence on the toxicity and efficacy profile of the combination. This was previously seen with the type 1 CD20 antibody ofatumumab, which was compared in a similar study design in a phase Ib/2 trial that found improved efficacy of the combination when ibrutinib was started first (Jaglowksi et al., 2012).

There are several viable hypotheses as to why sequence of administration with ibrutinib and obinutuzumab may be important. For example, ibrutinib causes lymphocytosis, which could increase the risk of infusion reactions to obinutuzumab but may also improve its efficacy. On the other hand, ibrutinib also mitigates the production of cytokines such as CCL3 and CCL4 which stimulate CLL cell proliferation, and therefore starting ibrutinib before obinutuzumab may actually decrease the rate of infusion reactions. Another possibility is that these effects *in vivo* are negligible and it is best to start the two drugs simultaneously for patient convenience.

Our study will help determine which (if any) of these sequences of administration are better in terms of safety and efficacy, which could help define the standard of care for administration of this combination in future studies and eventually in clinical practice.

2.4 Correlative Studies Background

BH3 Profiling

This study will incorporate a laboratory technique known as BH3 profiling, which is a functional assay we previously developed that detects the proximity of malignant cells to the threshold of apoptosis (what we call ‘priming’) through physiologic interrogation of BCL-2 family members (Ryan et al., 2010). To perform a BH3 profile, we add individual BH3-only peptides to gently permeabilized primary CLL cells and use fluorescence activated cell sorting (FACS) to determine the amount of mitochondrial depolarization induced by each peptide, as measured by cytochrome c release.

We previously found that in a small, heterogeneously treated cohort of CLL patients, increased priming was associated with improved clinical response (Davids et al., 2012). Building on these initial studies, we will incorporate BH3 profiling into this trial to determine whether priming predicts degree of clinical response in this larger, homogeneously treated patient population.

Genomic Markers

We will perform whole exome sequencing on CLL cells and normal tissue from patients at baseline to evaluate for somatic mutations that may confer drug sensitivity and resistance. Our group and others have recently identified recurrent somatic mutations in the CLL genome which appear to associate with prognosis; these include *NOTCH1* and *SF3B1* (Wang et al, 2011). At present, whether other recurrent mutations associate with prognosis is less clear, although our group also recently reported resistance to ibrutinib in vitro in patients carrying certain mutations in NFkB pathway genes (Improgo et al, 2012). Our group has also recently found that the presence of subclonal driver mutations was associated in a retrospective analysis with time to next treatment (Landau et al, 2013). In this trial, we will assess all of these recently described mutations as well as the presence of a subclonal driver mutation as potential predictors of response and progression-free survival. We will also bank samples at time of relapse for repeat analysis by whole exome sequencing to assess for the acquisition of resistance mutations.

We will also evaluate established CLL prognostic markers such as cytogenetics by FISH, *TP53* mutation, *IGHV* status, and *ZAP-70* status, and will determine whether these factors are associated with response to the ibrutinib plus obinutuzumab combination.

Sequentia Sequencing Studies

Although conventional MRD-testing in CLL provides reasonable sensitivity for residual disease detection, novel methods of MRD-detection promise to allow even more sensitive detection with the potential for better prognostic power. Sequentia, Inc. (South San Francisco, CA) has developed an assay known as LymphoSIGHT, in which a baseline sample of genomic DNA is extracted from tumor cells, amplified using locus-specific primer sets for *IGH* and *IGK* rearrangements, and sequenced. Once a patient achieves a MRD-negative state, a peripheral blood or bone marrow sample is examined to determine whether tumor DNA is still detectable. Our group has previously shown that this technique is feasible in patients with aggressive lymphoma (Armand et al., 2013), and we will now explore its utility in CLL by incorporating Sequentia MRD testing in parallel with conventional MRD testing for patients who achieve CR.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

Unless otherwise specified, laboratory tests required for eligibility must be completed within 2 weeks prior to study entry. Baseline tumor measurements by CT scan must be performed within 30 days of starting study treatment. Bone marrow biopsy within 3 months prior to study treatment will be acceptable if there has not been significant CLL-directed therapy given since the test was performed.

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

- 3.1.1 Must have a confirmed diagnosis of chronic lymphocytic leukemia or small lymphocytic lymphoma as per IW-CLL 2008 criteria (Hallek et al, 2008). Specifically, patients must also require therapy for that diagnosis, based on meeting at least one of the following criteria:
- evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin <11.0 g/L) and/or thrombocytopenia (platelets <100 x 10⁹/L)
 - massive (≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly
 - massive nodes (at least 10 cm longest diameter), progressive, or symptomatic lymphadenopathy
 - progressive lymphocytosis with an increase of more than 50% over a 2-month period or LDT of <6 months. Lymphocyte doubling time may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In subjects with initial blood lymphocyte counts of <30 x 10⁹/L, LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded
 - autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy (also see Exclusion Criteria, Section 3.2)
 - documented constitutional symptoms, defined as 1 or more of the following disease-related symptoms or signs:
 - unintentional weight loss >10% within 6 months prior to screening
 - significant fatigue (inability to work or perform usual activities)
 - fevers >100.5° F or 38.0° C for 2 or more weeks prior to screening without evidence of infection
 - night sweats for more than 1 month prior to screening without evidence of infection

- 3.1.2 Relapsed after or refractory to at least one prior CLL-directed therapy that was instituted due to patient previously meeting IWCLL 2008 criteria for treatment
- 3.1.3 Age greater than or equal to 18 years. Because CLL is extremely rare in persons <18 years of age, children are excluded from this study.
- 3.1.4 ECOG performance status ≤ 2 (see Appendix A)
- 3.1.5 Patients must meet the following hematologic criteria at screening, unless they have significant bone marrow involvement of CLL confirmed on biopsy:
 - Absolute neutrophil count ≥ 500 cells/mm³ ($0.5 \times 10^9/L$). Growth factor allowed to achieve
 - Platelet count $\geq 25,000$ cells/mm³ ($25 \times 10^9/L$) independent of transfusion within 7 days of screening
- 3.1.6 Adequate hepatic function defined as:
Serum aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 4.0 \times$ upper limit of normal (ULN), bilirubin $\leq 2.0 \times$ ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
- 3.1.7 Adequate renal function defined by serum creatinine $< 2.0 \times$ ULN unless due to biopsy proven CLL kidney infiltration
- 3.1.8 The effects of ibrutinib and obinutuzumab on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately
- 3.1.9 Patients who have undergone prior allogeneic transplantation are eligible provided that their transplant day 0 is > 6 months from their first dose of study drug
- 3.1.10 Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

- 3.2.1 Patients receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization) within 2 weeks of Cycle 1/Day 1 with the following exceptions:
 - Corticosteroid therapy (prednisone or equivalent ≤ 20 mg daily) is allowed as clinically warranted as long as the dose is stabilized at least for 7 days prior to initial dosing. Topical or inhaled corticosteroids are permitted.
 - Patients who may experience clinical deterioration may start therapy after a shorter washout period with prior approval by the PI
- 3.2.2 Post allo patients must not have active graft versus-host disease and be off all immune suppression (other than steroids, as above).
- 3.2.3 History of severe allergic or anaphylactic reactions to monoclonal antibody therapy
- 3.2.4 Prior treatment with either obinutuzumab or ibrutinib
- 3.2.5 History of other malignancies, except:
 - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
 - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
 - Adequately treated carcinoma in situ without evidence of disease.
 - Low-risk prostate cancer on active surveillance
- 3.2.6 Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone) within 28 days of the first dose of study drug.
- 3.2.7 Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
- 3.2.8 Recent infection requiring systemic treatment that was completed ≤ 7 days before the first dose of study drug.
- 3.2.9 Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.
- 3.2.10 History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- 3.2.11 Known history of human immunodeficiency virus (HIV) or active hepatitis C virus (HCV) or hepatitis B virus (HBV). *Patients who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.*
- 3.2.12 Any uncontrolled active systemic infection.
- 3.2.13 Major surgery within 4 weeks of first dose of study drug.
- 3.2.14 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.

- 3.2.15 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 randomization.
- 3.2.16 Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
- 3.2.17 Lactating or pregnant.
- 3.2.18 Unwilling or unable to participate in all required study evaluations and procedures. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations)
- 3.2.19 Patients receiving any other study agents
- 3.2.20 Patients with known CNS involvement
- 3.2.21 Baseline QTcF >480 ms. NOTE: This criterion does not apply to patients with a left bundle branch block.
- 3.2.22 Patients who require warfarin or other vitamin K antagonists for anticoagulation (other anticoagulants are allowed after consultation with the Principal Investigator).
- 3.2.23 Concurrent administration of medications or foods that are strong inhibitors or inducers of CYP3A (see Appendix B).
- 3.2.24 Patients with ongoing use of prophylactic antibiotics are eligible as long as there is no evidence of active infection and the antibiotic is not included on the list of prohibited medications
- 3.2.25 Significant co-morbid condition or disease which in the judgment of the Principal Investigator would place the patient at undue risk or interfere with the study

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Office of Data Quality (ODQ) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the ODQ protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the ODQ Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The ODQ registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the ODQ registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.
- Complete the ODQ protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for a treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the ODQ at 617-632-2295.
- The ODQ Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Dana-Farber Cancer Institute by the Study Coordinator. All sites should call or email the project manager at 617-632-3539 to verify slot availabilities.

Following registration, participants should begin protocol therapy as soon as possible after enrollment. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and faxed (617-632-5152) or e-mailed (asavell@partners.org) to the Lead Site Project Manager:

- Copy of relevant medical records
- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist
- Registration Form

The research nurse or data manager at the participating site will then call 617-632-3539 or e-mail Alexandra Savell at asavell@partners.org to verify eligibility. To complete the registration process, the Project Manager will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. The Project Manager will fax or e-mail the participant study number, the arm assignment, to the participating site.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

NOTE: Registration and randomization can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC.

5. TREATMENT PLAN

5.1 Treatment Regimen

Ibrutinib and obinutuzumab will be administered as per their respective labels, with 28 consecutive days defined as a treatment cycle. Treatment will generally be administered on an outpatient basis. On days when patients receive both ibrutinib and obinutuzumab, ibrutinib will be given prior to obinutuzumab. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Subjects will be randomly assigned to each of three dose sequence arms, as follows:

- Cohort A (10 patients): obinutuzumab x 1 cycle → obinutuzumab + ibrutinib x total of 6 cycles of obinutuzumab → ibrutinib until progression or unacceptable toxicity
- Cohort B (10 patients): ibrutinib x 1 cycle → obinutuzumab + ibrutinib x total of 6 cycles of obinutuzumab → ibrutinib until progression or unacceptable toxicity
- Cohort C (10 patients): obinutuzumab + ibrutinib started simultaneously x total of 6 cycles of obinutuzumab → ibrutinib until progression or unacceptable toxicity

If an arm meets the safety criteria as described in Section 13, 10 additional patients will be accrued to an expansion phase of each arm to obtain additional safety and efficacy data.

Ibrutinib

The participant will be requested to maintain a medication diary of each dose of ibrutinib. The medication diary will be returned to clinic staff at the end of each cycle.

<i>Agent</i>	<i>Premedications; Precautions</i>	<i>Dose</i>	<i>Route</i>	<i>Schedule</i>	<i>Cycle Length</i>
Ibrutinib	May be taken with or without food	420 mg	PO	Daily, days 1-28	28 days (4 weeks)

Obinutuzumab:

Patients should receive the following pre-medications prior to each obinutuzumab infusion:

- Diphenhydramine 50 mg IV prior to the first two doses, then 25-50 mg IV or PO as tolerated for subsequent doses
- Methylprednisolone 80 mg IV
- Acetaminophen 1,000 mg PO

Alternatively, sites may also follow their standard of care for pre-medication for obinutuzumab.

Cycle and Day of Administration*		Dose of Obinutuzumab	Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)
Cycle 1	Day 1	100 mg	Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hour. The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.
	Day 15	1000 mg	
Cycles 2–6	Day 1	1000 mg	

* Depending on treatment arm, first cycle of obinutuzumab may start in treatment Cycle 1 or Cycle 2.

5.2 Randomization

Patients will be randomized in a 1:1:1 ratio using the permuted block algorithm within stratum. Randomization will be stratified by age (≥ 65 vs < 65) and 17p- status. If an arm is terminated after the first stage, the randomization will take place for the remaining arms in a 1:1 ratio.

5.3 Pre-Treatment Criteria

5.3.1 Cycle 1, Day 1

Participants must meet all of the inclusion criteria, have none of the exclusion criteria, and must be registered to the protocol prior to initiating therapy.

C1D1 laboratory results need not meet eligibility parameters again provided that they met criteria at screening and in the opinion of the treating investigator do not pose any undue risk to the participant.

5.3.2 Subsequent Cycles

5.3.2.1 ANC must be $\geq 500/\text{mm}^3$ if growth factor is not administered. If growth factor is administered on the day of treatment, the participant may proceed with treatment at the investigator's discretion.

5.3.2.2 Platelet count must be $\geq 10\text{K}$

5.3.2.3 All non-hematologic toxicities must have resolved to $\leq$ Grade 2, or to the patient's baseline condition

5.4 Agent Administration

5.4.1 Ibrutinib

Ibrutinib 420 mg will be administered orally once daily and given in continuous 28 day cycles. The first dose of ibrutinib 420 mg (3 x 140-mg capsules) will be administered in the clinic, with subsequent doses self-administered by subjects at home. Ibrutinib should be administered with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. Each dose of ibrutinib should be taken at approximately the same time each day. Ibrutinib may be administered without regard to meals. Ingestion of grapefruit and Seville oranges should be avoided for the duration of ibrutinib treatment due to CYP3A inhibition. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day, with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose. Treatment will continue until disease progression, adverse event requiring discontinuation, subject withdrawal, or death.

The date, time, and quantity of drug taken will be recorded in a drug self-administration diary. Patients should record any deviation from taking the full daily dose (e.g., vomited doses, missed doses, doses reduced due to missing or lost capsules). Missed doses outside the windows defined above or vomited doses should not be taken or repeated. At each visit, a sufficient number of doses will be dispensed so that the patient will have the required number of doses until the next visit, taking into account the window for the next visit.

5.4.2 Obinutuzumab

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

- During the first cycle it is administered, Day 1, 100 mg obinutuzumab will be administered
 - Day 2, 900 mg of obinutuzumab will be administered
 - Days 8 and 15, 1000 mg of obinutuzumab will be administered.
- During the second through sixth cycles of obinutuzumab, 1000 mg will be administered on day 1

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision by a clinician 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. There will be 1 hour observation following Obinutuzumab infusion in Cycle 1, and observation may be waived if participant has tolerated previous infusions without issue beginning with Cycle 2.

For patients who experience a significant obinutuzumab infusion reaction, it is permitted to treat patients with an obinutuzumab desensitization protocol as per institutional standards, provided that this is approved by the PI (or the senior investigator) and that the desensitization is done in collaboration with an allergist.

Premedication Requirements

Infusion-Related Reactions

All infusion reactions experienced by participants on study must be reported to the Lead Study team and Overall PI as soon as feasible as part of additional mandatory reporting requirements.

Since some patients may develop hypersensitivity or other IRRs to obinutuzumab, pre-medication is recommended to reduce the risk of infusion reactions as outlined below.

Alternatively, sites may also follow their local standard of care for pre-medication for obinutuzumab.

- First cycle of obinutuzumab, Days 1 and 2, all patients require pre-medication with:
 - IV glucocorticoid: methylprednisolone (80 mg) 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.
 - Oral acetaminophen (1000 mg) and IV diphenhydramine (50 mg) administered at least 30 minutes before starting each obinutuzumab infusion.
- First cycle of obinutuzumab, Days 8 and 15 and Cycles 2-6, Day 1:
 - All patients require pre-medication with oral acetaminophen (1000 mg) 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 (25-50 mg) administered at least 30 minutes before starting each subsequent obinutuzumab infusion.
 - Patients who experience a Grade 3 IRR with the previous infusion or who have lymphocyte counts of $\geq 25 \times 10^9/L$ prior to the next treatment will require pre medication with IV glucocorticoid: methylprednisolone (80 mg) 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 treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their hypertensive medication.

Obinutuzumab Dosing

The first 1000 mg of obinutuzumab will be administered over 2 days. During Cycle 1, Day 1, 100 mg will be administered. On the following day (Cycle 1, Day 2), 900 mg will be administered (see obinutuzumab regimen in Section 5.1).

If a patient experiences any grade infusion reaction during infusion, adjust the infusion as outlined below:

- Grade 4 (life threatening): Stop infusion and discontinue therapy.
- Grade 3 (severe): Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.
- Grade 1 – 2 (mild to moderate): Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if patient does not experience any infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.

5.5 Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting toxicity (DLT) is defined as below.

Toxicity will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (<http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE>) with the exceptions recommended by the IWCLL guidelines for the diagnosis and treatment of CLL defined in Appendix D.

Toxicity will be considered dose-limiting if it occurs during the first two cycles of combination therapy of obinutuzumab and ibrutinib, and is considered at least possibly related to either study drug. Any event defined below during this time period, unless the investigator considers the event clearly unrelated to study drug or due to extraneous causes, will be considered a dose-limiting toxicity.

Dose-limiting toxicities will be defined as the following:

- Grade 4 anemia; Grade 4 neutropenia lasting >7 days (while receiving growth factor support); Grade 4 thrombocytopenia lasting > 7 days; Grade ≥ 3 febrile neutropenia; and Grade ≥ 3 thrombocytopenia with Grade >2 hemorrhage;
 - For patients with CLL/SLL, hematologic toxicity will be graded according to CTCAE guidelines (Appendix C) and Grade 4 toxicity lasting >7 days will be considered dose limiting; this will not apply to CLL/SLL patients who are not evaluable for hematologic toxicity by CTCAE criteria (see

Appendix C)

- Grade ≥ 3 non-hematologic toxicity unresponsive to standard supportive care measure with the exception of:
 - Asymptomatic Grade ≥ 3 lab abnormalities that resolve to $\leq$ Grade 1 or baseline within 7 days;
 - Grade 3 infusion reactions and grade 3 infections
- AST or ALT $> 3x$ upper limit of normal with concomitant elevation of total bilirubin $> 2x$ upper limit of normal
- Treatment delay of ≥ 4 weeks due to unresolved toxicity; and
- Non-hematologic toxicity of Grade 2 (at any time during treatment) that, in the judgment of the overall principal investigator is dose-limiting.

Adverse events meeting the above definitions but are clearly unrelated to study drug will not be considered DLTs. This is justifiable in this study given the extensive experience with both drugs, both of which are FDA approved. In rare instances an event may fall within the definition of a DLT as defined above but the event may not be considered a DLT (i.e., not clinically meaningful/significant). If this occurs, the reasons for not considering the event a DLT will be clearly documented with supporting rationale. In addition, other events may occur which do not meet the definition of a DLT but are concerning to the Principal Investigator or other Investigator(s) may be considered to be DLTs. Serious adverse events that occur after the first 2 cycles of combination therapy will not count formally as DLTs but will be included in the safety analysis to determine which cohort to take to dose expansion.

5.5.1 Assessment of Dosing-Limiting Toxicity

Patient will be evaluable for DLT if the patient starts the first cycle of the combination therapy. Although it is very unlikely based on previous reports on monotherapy, if a patient develops a DLT during the first cycle of the monotherapy, this patient will remain for the safety analysis but will be regarded as unevaluable for the DLT assessment of the combination therapy since the study objective is to choose an optimal schedule of the combination therapy. Patients who discontinue treatment early due to disease progression or withdrawal will be asked to have all end-of-treatment safety evaluations performed as described in the protocol. If a patient withdraws from treatment prior to completing the first cycle of combination treatment due to any reason other than DLT or disease progression and does not meet the minimum requirements for inclusion in the DLT-determining population described above, that patient will be regarded as unevaluable for the DLT assessment but remain in the study for the safety analysis. At the conclusion of the study, both the DLT assessment and safety analysis will be considered in order to determine which dosing schedule will be used for the future study.

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

5.6 General Concomitant Medication and Supportive Care Guidelines

5.6.1 Supportive Care

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, hematopoietic growth factors, analgesics, and antiemetics when appropriate.

White cell growth factor support with Neulasta, Neupogen, or tbo-filgrastim (Granix) will be administered at the discretion of the treating investigators. Neulasta will be administered at 6 mg SC x 1. Alternatively, Neupogen may be substituted at the discretion of the treating investigator and administered at 300-480 mcg SC daily. Granix may also be used, with dosing capped at 300 mcg. Neulasta, Neupogen, and Granix will be from commercial supply.

5.6.2 Tumor Lysis Syndrome (TLS) Prophylaxis

Though relatively rare in CLL, tumor lysis syndrome (TLS), characterized by hyperkalemia, hyperuricemia, and hyperphosphatemia resulting from the rapid release of potassium, uric acid, and phosphate, has been reported in patients with CLL, necessitating TLS prophylaxis including allopurinol and oral or IV hydration.

The risk of TLS is highest during the first two cycles of therapy. It is recommended that allopurinol 300mg PO daily begin at least 3 days before the start of therapy, and continue through the end of the first cycle of combination therapy. Subjects with an allopurinol allergy should receive alternative TLS prophylaxis if possible. All subjects should be instructed to maintain adequate hydration and maintain urinary output as an additional measure to prevent TLS. Hydration levels should be adjusted according to age and clinical status, and lowered if the subject's cardiovascular status indicates the possibility of volume overload. Based on clinical and laboratory parameters, TLS prophylaxis may be continued or restarted as needed at the investigator's discretion.

5.6.3 Treatment and Dose Modification for Tumor Lysis Syndrome

All subjects meeting criteria of laboratory TLS or $\geq$ Grade 1 TLS according to the Cairo-Bishop Definition of Tumor Lysis Syndrome should receive vigorous intravenous hydration and should be considered for rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities. See Section 6.2, Dose Modification Table, for additional instructions.

5.6.4 Prophylactic Antibiotics

Prophylaxis for *Pneumocystis jiroveci* pneumonia (PJP) with Bactrim or equivalent, and anti-herpetic viral prophylaxis with acyclovir or equivalent is mandatory for all patients. It is recommended that patients receive both prophylactic medications at the beginning of therapy (regardless of Arm), and to continue for as long as the patient is receiving ibrutinib.

5.6.5 Drug-Drug Interactions

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

5.7 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with [REGIST-OP-1](#).

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Matthew S. Davids, MD at 617-632-6331, DFCI pager 57215.

5.8 Duration of Follow Up

After removal from protocol therapy, participants will be followed until start of a new CLL-directed therapy, or death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event in addition to being followed until start of a new CLL-directed therapy.

Follow up/survival follow up may take place over the phone, or other secure method of direct contact with the participant.

5.9 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Start of new CLL-directed therapy
- Disease Progression
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with [REGIST-OP-1](#).

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1.1 Adverse Event List(s) for Ibrutinib

For a detailed description of the toxicity profile of ibrutinib in clinical trials, please see section 7.1.1.1. A detailed adverse event list can also be found in the ibrutinib label.

6.1.2 Adverse Event List(s) for Obinutuzumab

For a detailed description of the toxicity profile of obinutuzumab in clinical trials, please see section 7.1.1.2. A detailed adverse event list can also be found in the obinutuzumab label.

Treatment-Related Lymphocytosis

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood. Upon initiation of treatment, a transient phase of increase in lymphocyte counts (ie, $\geq 50\%$ increase from baseline and above absolute count 5,000/ μL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings. Lymphocytosis occurs typically during the first few weeks of ibrutinib therapy (median time 1.1 weeks), and

resolves within a median of 18.7 weeks in CLL. A substantial increase in the number of circulating lymphocytes has been observed in a subset of patients. There have been cases of leukostasis reported in a small number of mantle cell lymphoma patients treated with ibrutinib, though this has not been observed in CLL. A high number of circulating malignant cells ($>400,000/\mu\text{L}$) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration as indicated. In cases of extreme lymphocytosis, ibrutinib may be temporarily held after discussion with the Principal Investigator.

Treatment of Overdose

In the case of overdose, clinic staff should be notified immediately and supportive care is to be given as indicated. Patients should be informed to contact their doctor immediately if they have taken an overdose and should stop taking ibrutinib.

6.2 Dose Modifications/Delays

Dose delays and modifications will be made using the recommendations below. Dose reductions to ibrutinib will be made as per section 6.2.1. Dose reductions of obinutuzumab will not be permitted.

Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Patients will be monitored continuously for toxicity while on study therapy. Hematologic and non-hematologic Toxicity will be assessed using the NCI-CTCAE Version 4.0. If a patient has an adverse event of grade 3 or 4 severity that is thought to be at least likely due to ibrutinib, then ibrutinib dose modifications can be considered after discussion with the principal investigator, using Table 1 as suggested guidelines. There should be no attempt to make up for doses omitted due to toxicity.

Dosing of ibrutinib and obinutuzumab may be withheld up to 4 weeks for toxicity. Doses withheld for > 4 weeks due to toxicity at least possibly related to study drug will result in discontinuation from the study. Any patient who requires > 2 dose reductions of ibrutinib due to toxicity over the course of the study will be discontinued from the study.

Participants who require dose hold of either or both drugs for >4 weeks may only do so after discussion and subsequent documented approval by the Overall PI.

When treatment is delayed, the patient should be kept on the original schedule of assessments.

6.2.1 Dose modification

Dose delays of obinutuzumab and dose delays or modifications of ibrutinib may be made as per tables 1 and 2 if a toxicity is believed to be at least likely or definitely related to the study drugs.

6.2.1.1 Hematologic Toxicity

Table 1 Dose Modifications for Hematologic and Non-Hematologic Toxicity

Once the symptoms of the adverse reaction have resolved to grade 1 or baseline (recovery), resume ibrutinib therapy at the recommended dose per table 1.

Table 1. Recommended Dosage Modifications for Adverse Reactions (ibrutinib)

Adverse Reaction^{a,b}	Occurrence	Dose Modification for CLL/SLL After Recovery Starting Dose = 420 mg
Grade 2 cardiac failure	First	Restart at 280 mg daily ^c
	Second	Restart at 140 mg daily ^c
	Third	Discontinue ibrutinib
Grade 3 cardiac arrhythmias	First	Restart at 280 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 280 mg daily
	Second	Restart at 140 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.

Table 2. Recommended Dosage Modifications for Adverse Reactions (obinutuzumab)

Worst CTCAE Grade Toxicity	Recommended Action to be Taken
<i>Neutropenia (ANC)</i>	
Grade 1	Maintain dose level
Grade 2	First incidence: Maintain dose level Second incidence: Consider growth factor support
Grade 3 / 4 <i>1st Occurrence</i>	Hold obinutuzumab until resolved to $\leq$ Grade 2 or baseline, consider growth factor support.
Grade 3 / 4 <i>Subsequent Occurrences</i>	Hold obinutuzumab until resolved to $\leq$ Grade 2 or baseline, consider growth factor support.
<i>Thrombocytopenia</i>	
Grades 1,2, and 3 with no evidence of bleeding	Maintain dose level
Grade ≥ 3 thrombocytopenia with Grade >2 bleeding	Hold both obinutuzumab until to $\leq$ Grade 2 or baseline and bleeding resolves, consider platelet transfusion as necessary.
Grade 4 <i>1st Occurrence</i>	Hold both obinutuzumab until to $\leq$ Grade 2 or baseline, consider platelet transfusion as necessary.
Grade 4 <i>Subsequent Occurrences</i>	Hold both obinutuzumab until to $\leq$ Grade 2 or baseline, consider platelet transfusion as necessary.

****If pancytopenic at baseline, follow IWCLL guidelines for grading hematologic toxicities (Appendix C).**

Dose changes must be recorded in the Dose Administration CRF.

6.2.2 Peri-operative dosing of ibrutinib

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, Ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without significant serosanguinous drainage or the need for drainage tubes.
- 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.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events Lists

7.1.1.1 Adverse Event List for Ibrutinib

Summary of Clinical Safety Data for Ibrutinib

With regard to safety in clinical trials, the integrated safety profile of ibrutinib administered as monotherapy to 506 subjects across 8 company-sponsored clinical studies (PCYC-04753, PCYC-1102-CA, PCYC-1104-CA, and PCYC-1106-CA, PCI32765MCL2001, PCYC-1111-CA, PCYC-1117-CA, and PCI-32765-JPN-101) has been evaluated (reference: Investigator's Brochure Version 7, dated 31 July 2013). The most common treatment-emergent adverse events as of 06 April 2013 were diarrhea (42.1%), fatigue (33.8%), nausea (26.1%), cough (20.2%), and peripheral edema (18.6%). Grade 3 or higher adverse events were experienced by 60.7% of subjects, the most common (> 2%) of which were hematologic in nature: neutropenia (9.7%), thrombocytopenia (6.5%), and anemia (4.9%). Pneumonia (7.7%) was the most frequent non-hematologic Grade 3 or higher adverse event.

Serious adverse events were experienced by 46.4% of treated subjects. The only serious events occurring in more than 2% of subjects (excluding disease progression) were pneumonia (7.9%), atrial fibrillation (3.2%), and febrile neutropenia (2.8%).

In addition, data is available from combination therapy clinical studies. Refer to the latest version of the IB for more details.

Safety data are available for 636 subjects treated in 8 company-sponsored monotherapy and 3 combination therapy studies, as discussed below (Investigator's Brochure Version 7, dated 31 July 2013).

Monotherapy Studies

The integrated safety profile of ibrutinib administered as monotherapy to 506 subjects across 8 clinical studies (PCYC-04753, PCYC-1102-CA, PCYC-1104-CA, and PCYC-1106-CA, PCI32765MCL2001, PCYC-1111-CA, PCYC-1117-CA, and PCI-32765-JPN-101) has been evaluated. The most common treatment-emergent adverse events as of 06 April 2013 were diarrhea (42.1%), fatigue (33.8%), nausea (26.1%), cough (20.2%), and peripheral edema (18.6%). Grade 3 or higher adverse events were experienced by 60.7% of subjects, the most

common (> 2%) of which were hematologic in nature: neutropenia (9.7%), thrombocytopenia (6.5%), and anemia (4.9%). Pneumonia (7.7%) was the most frequent non-hematologic Grade 3 or higher adverse event.

Serious adverse events were experienced by 46.4% of treated subjects. The only serious events occurring in more than 2% of subjects (excluding disease progression) were pneumonia (7.9%), atrial fibrillation (3.2%), and febrile neutropenia (2.8%).

Combination Therapy Studies

The safety of ibrutinib administered as combination therapy to 130 subjects was evaluated in 3 clinical studies: PCYC-1108-CA PCYC-1109-CA, and PCI32765DBL1002. In Study PCYC-1108-CA, ibrutinib is administered in combination with either the FCR or the BR regimen chemotherapy. In Study PCYC-1109-CA, ibrutinib is administered in combination with the monoclonal antibody ofatumumab in patients with relapsed and refractory CLL. In Study PCI-32765DBL1002, ibrutinib is administered in combination with standard R CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone).

Across these combination studies, the most common adverse event has been diarrhea (47.7%); nausea (33.1%), infusion related reaction (29.2%), and fatigue (26.2%). Neutropenia (24.6%) has been the most common hematologic toxicity, followed by anemia (20.0%) and thrombocytopenia (19.2%).

Adverse events that were Grades 3 or higher in severity were reported in 57.7% of subjects. The most common have been hematologic: neutropenia (21.5%), anemia and thrombocytopenia (7.7% each), and febrile neutropenia (6.2%). Pneumonia (7.7%) was the most frequently reported non-hematologic Grade 3 or higher adverse event.

Overall, 36.2% of treated subjects have experienced at least 1 serious adverse event. The most commonly reported serious adverse events were febrile neutropenia and pneumonia (6.2% each), cellulitis (3.8%), atrial fibrillation (3.1%), and dehydration and dyspnea (2.3% each).

Treatment Discontinuations

As of 6 April 2013, 71/636 subjects discontinued treatment due to an adverse event, across the monotherapy and combination therapy ibrutinib studies (excluding Study PCYC-1103-CA); 62 subjects receiving monotherapy population and 9 subjects receiving combination therapy. The most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), cardiac arrest (3 subjects) and Richter's Syndrome (3 subjects).

Hemorrhagic Events

There are reports of hemorrhagic events in subjects treated with ibrutinib in both monotherapy and combination clinical studies. The majority of these hemorrhagic adverse events were of Grade 1 or 2 in severity, including minor hemorrhagic events like contusion, epistaxis and

petechiae; and major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage and hematuria. Hemorrhagic events of Grade 3 or higher, including central nervous system hemorrhage of any grade severity, occurred in 3.4% (17/506) of subjects treated in monotherapy studies and in 3.1% (4/130) of subjects treated in combination therapy studies. And none were reported in any healthy volunteer studies (n=100).

Due to multiple confounding factors (such as older age, advanced stage cancer, comorbidities, and concomitant medication usage), it is unclear whether or not these hemorrhagic events were attributable to ibrutinib.

Subjects were excluded from participation in ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Do not administer ibrutinib concomitantly with warfarin or other vitamin K antagonists. Ibrutinib should be used with caution in patients requiring other anticoagulants or medications that inhibit platelet function. Patients receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising and ibrutinib should be withheld in the event of any bleeding events. Supplements such as fish oil and vitamin E preparations should be avoided. Patients with congenital bleeding diathesis have not been studied.

Subjects in the current study will be monitored closely for hemorrhagic adverse events. 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. (Please refer to prohibitions and restrictions for further details)

Cardiac

Atrial fibrillation and/or atrial flutter have been reported in patients treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Subjects with a history of cardiac arrhythmias should be monitored closely.

Rash

Mild to moderate rashes have been observed with ibrutinib alone or in combination with other drugs. A single case of Stevens-Johnson Syndrome (SJS) was reported in a male subject with CLL treated with ibrutinib 420 mg/day. The subject was also receiving multiple concomitant medications known to be associated with SJS. Subjects should be monitored closely for signs and symptoms suggestive of SJS.

Other Malignancies

Other malignant diseases have been observed in subjects who have been treated with ibrutinib, including skin cancers, other carcinomas, and other hematologic malignancies. It is not clear whether or not these events are attributable to ibrutinib. Subjects in the current study will be monitored for other malignancies.

Infection

In non-randomized clinical trials, infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects with MCL ($\geq$ Grade 3; 25.2%) and CLL/SLL ($\geq$ Grade 3; 37.6%). Some of these infections have been associated with hospitalization and death. Subjects should be monitored for fever and infections and appropriate anti-infective therapy should be instituted as indicated.

Treatment related Lymphocytosis

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood. Upon initiation of treatment, a transient phase of increase in lymphocyte counts (i.e., $\geq 50\%$ increase from baseline and above absolute count 5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings. Lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and resolves within a median of 18.7 weeks in CLL patients. A substantial increase in the number of circulating lymphocytes (e.g., $> 400,000/\text{mcL}$) has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients with mantle cell lymphoma (though not CLL) treated with ibrutinib. A high number of circulating malignant cells ($> 400,000/\text{mcL}$) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration and/or leukaphoresis may be considered, and the principal investigator should be contacted.

7.1.1.2.2 Treatment of Overdose

In the case of overdose, clinic staff should be notified immediately and supportive care is to be given as indicated. Patients should be informed to contact their doctor immediately if they have taken an overdose and should stop taking ibrutinib.

Additional toxicity information is detailed in the package insert.

7.1.1.2 Adverse Event List for Obinutuzumab

Summary of Clinical Safety of Obinutuzumab

Obinutuzumab has been administered to over 1,310 patients with CD20-positive malignancies. Both in patients with NHL and with CLL, IRR was the most common AE in clinical trials conducted to date. They were predominantly associated with the first infusion, generally occurring early during the infusion, shortly after, or in some cases up to 24 hours after the completion of the infusion with obinutuzumab. The incidence and intensity of IRRs decreased with subsequent infusions of obinutuzumab. In a few patients, concurrent signs of tumor lysis

syndrome (TLS) were observed. Other frequently observed AEs include infections and neutropenia. These events appeared to be more common in patients with CLL compared to NHL.

In trials investigating the combination of obinutuzumab and CHOP, FC, chlorambucil or bendamustine, the incidence of AEs in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. So far, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of AEs have been determined.

A pooled analysis of safety data for obinutuzumab collected during the monotherapy studies BO20999 and BO21003 was conducted in patients with NHL (aggressive [aNHL] and indolent [iNHL]) or CLL who participated in those two studies (both Phase I and Phase II) and received monotherapy treatment with obinutuzumab and included a total 205 patients with NHL (49 aNHL and 156 iNHL patients) and 38 patients with CLL.

In the group of 38 patients with CLL treated with obinutuzumab monotherapy, the majority of patients (25 [66%]) were treated for ≥ 4 weeks to < 6 months. Eleven patients (29%) were exposed for 6 to < 12 months, and two patients (5%) were exposed for 12 months or longer. Eight of 38 patients (21%) with CLL were withdrawn during the treatment phase; 4 patients (11%) were withdrawn due to AEs, which indicates that AEs were mostly manageable. Almost all patients (37/38 [97%]) experienced an IRR. The number of patients with Grade 3–4 IRRs was 11/38 (29%). As is typical for patients with CLL, blood and lymphatic system disorders were among the most frequently reported AEs, in particular neutropenia (13/38 patients [34%]), febrile neutropenia (5/38 patients [13%]), and thrombocytopenia (7/38 patients [18%]).

Infections and infestations were common AEs, occurring in 21/38 patients (55%). Infections reported in more than one patient were nasopharyngitis (6 patients), bronchitis and sinusitis (4 patients each), influenza and lung infection (3 patients each), and herpes zoster and oral herpes (2 patients each).

Thirteen patients (34%) died, 8 of these due to disease progression. One patient died from an unspecified cause after withdrawal from the study for lack of response. This patient had received subsequent experimental therapies and had stable CLL at the time she died. For 4 additional patients, the cause of death was reported as colon cancer, lung adenocarcinoma, metastasis, and septic shock, and all were considered not to be related to treatment.

In the two studies investigating obinutuzumab as monotherapy, BO20999 and BO21003, patients with CLL appeared to be at a higher risk of experiencing an AE of special interest than patients with NHL. The largest difference in the incidences was seen for neutropenia (occurring in 47% of patients with CLL [18/38] vs. 8% of patients with aNHL [4/49] and 8% of patients with iNHL [13/156]) and treatment-related AEs associated with the infusion (100% [38/38] vs. 80% [39/49] and 83% [129/156]).

To date, a very small number of patients have experienced TLS (six in total); four patients in the aNHL population (population including MCL) and one patient each in the CLL and iNHL populations.

Infections have been reported in 20/49 aNHL patients (41%), 74/156 iNHL patients (47%), and 21/38 CLL patients (55%). One iNHL patient was withdrawn from the study because of an infection. In addition, one CLL patient and one iNHL patient died from an infection (septic shock in both cases) during survival follow-up 671 days and 494 days after last dose of treatment, respectively.

Three CLL and 3 iNHL patients were withdrawn from treatment due to an AE of special interest, all for IRRs. An additional patient in the iNHL group discontinued treatment because of an infection. This indicates that these events were generally manageable.

In the Phase III Study BO21004 (CLL11), comparison of obinutuzumab + chlorambucil to chlorambucil alone showed that the most common AEs (all grades, Grades 3 – 4), respectively, were IRRs (69% vs. 0, 21% vs. 0), neutropenia (40% vs. 18%, 34% vs. 16%), thrombocytopenia (15% vs. 7%, 11% vs. 3%), anemia (12% vs. 10%, 4% vs. 5%), leukopenia (7% vs. 0, 5% vs. 0), pyrexia (10% vs. 7%, < 1 vs. 0), and cough (10% vs. 7%, 0 vs. < 1%).

The incidence of IRRs was 69% with the first infusion of obinutuzumab. The incidence of Grade 3 or 4 IRRs was 21%, with 8% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3%, with the second 1000-mg dose and <1% thereafter. No Grade 3 or 4 IRRs were reported beyond the first 1000-mg infusion. Of the first 53 patients receiving obinutuzumab in the trial, 47 (89%) experienced an IRR. After this occurrence, study protocol modifications were made to require pre-medication with a corticosteroid, antihistamine, and acetaminophen. The first dose was also divided into two infusions (100 mg on Day 1 and 900 mg on Day 2). Of the 45 patients for whom these mitigation measures were implemented, 21 patients (47%) experienced a reaction with the first 1000-mg dose and <2% thereafter.

The incidence of neutropenia reported as an AE was 40% in the obinutuzumab-treated arm and 18% in the chlorambucil-alone arm, with the incidence of SAEs being 1% and 0%, respectively. Cases of late-onset neutropenia (occurring 28 days after completion of treatment or later) were 16% in the obinutuzumab-treated arm and 12% in the chlorambucil-alone arm.

The incidence of infections was similar between arms. Thirty-eight percent of patients in the obinutuzumab-treated arm experienced an infection, 9% were Grade 3 – 4, and none were fatal.

The incidence of thrombocytopenia reported as an AE was 15% in the obinutuzumab-treated arm and 7% in the chlorambucil-alone arm. Five percent of patients in the obinutuzumab-treated arm experienced acute thrombocytopenia (occurring within 24 hours after the obinutuzumab infusion).

The incidence of Grade 3 or 4 tumor lysis syndrome was 2% in the obinutuzumab-treated arm vs. 0% in the chlorambucil-alone arm.

AEs related to musculoskeletal disorders, including pain (System Organ Class), have been reported with obinutuzumab with higher incidence than with the comparator (17% vs. 13%, respectively) (Goede et al. 2013).

Specific Adverse Events Associated With 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.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with obinutuzumab. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring, and consider HBV antiviral therapy.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with obinutuzumab. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following completion of therapy.

In patients who develop reactivation of HBV while receiving obinutuzumab, immediately discontinue obinutuzumab and any concomitant chemotherapy, and institute appropriate treatment. Resumption of obinutuzumab in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming obinutuzumab in patients who develop HBV reactivation.

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 magnetic resonance imaging (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 IRRs. Two-thirds of patients experienced a reaction to the first 1000 mg of obinutuzumab infusion. IRRs can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, and laryngeal edema). Other common symptoms include nausea, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Pre-medicate patients with acetaminophen, antihistamine, and a glucocorticoid. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs as needed. Closely monitor patients during the entire infusion. IRRs within 24 hours of receiving obinutuzumab have occurred.

For patients with any Grade 4 IRRs, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction, stop the obinutuzumab infusion. Permanently discontinue obinutuzumab therapy.

For patients with Grade 1, 2, or 3 IRRs, interrupt obinutuzumab for Grade 3 reactions until resolution of symptoms. Interrupt or reduce the rate of the infusion for Grade 1 or 2 reactions and manage symptoms.

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

Tumor Lysis Syndrome

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia from TLS can occur within 12 – 24 hours after the first infusion. Patients with high tumor burden and/or high circulating lymphocyte count ($> 25 \times 10^9/L$) are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol) and hydration beginning 12 – 24 hours prior to the infusion of obinutuzumab. For treatment of

TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Infection

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. 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

Obinutuzumab in combination with chlorambucil caused Grade 3 or 4 neutropenia in 34% of patients in clinical trials. 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).

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

Thrombocytopenia

Obinutuzumab in combination with chlorambucil caused Grade 3 or 4 thrombocytopenia in 12% of patients in clinical trials. In 5% of patients, obinutuzumab caused an acute thrombocytopenia occurring within 24 hours after the obinutuzumab infusion. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution. Transfusion of blood products (i.e., platelet transfusion) may be necessary.

Additional toxicity information is detailed in the package insert.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
- **For expedited reporting purposes only:**
 - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
 - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-

Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form within 1 business day after learning of the event.

All adverse events and SAEs will be assessed and documented up to 3 years on study. For those patients who continue to stay on study taking commercial ibrutinib maintenance for longer than 3 years since starting on study, we will collect only reportable AEs and SAEs.

In addition, all infusion reactions must be reported to the Overall PI and Lead Site contact by email regardless of grade as soon as feasible. They must also be entered into the database, and reported via expedited means if the event meets criteria in section 7.3.4.

7.3.1 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

- 7.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, all grade 4 unexpected toxicities, all grade 5 (death) regardless of study phase or attribution.

7.3.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs			
	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Unexpected**	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	Not required	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.				
* For participants enrolled and actively participating in the study <i>or</i> for AEs occurring within 30 days of the last intervention, the AE should be reported within <u>1 business day</u> of learning of the event. ** Events that are expected (event term), but were experienced at a more severe grade, or longer duration should also be reported as this is considered unexpected				

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the

toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

7.7 Expedited and Routine Reporting of Serious Adverse Events and Adverse Events of Special Interest to Genentech

7.7.1 Definition of Adverse Events

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

This includes the following:

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

7.7.2 Definition of Serious Adverse Events

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

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational medical product
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.7.3 Adverse Event Reporting Period

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).

The study period during which AEs and SAEs as described in the section above, where the patient has been exposed to Obinutuzumab must be reported. The reporting period begins after informed consent is obtained and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to the study treatment.

7.7.4 Assessments 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.

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

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the obinutuzumab, 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; and/or the AE abates or resolves upon discontinuation of the obinutuzumab or dose reduction and, if applicable, reappears upon re- challenge.

No

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

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This

includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

7.8 Procedures for Eliciting, Recording, and Reporting Adverse Events

7.8.1 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 clinical visit?”
- “Have you had any new or changed health problems since you were last here?”

7.8.2 Specific Instructions for Recording Adverse Events

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

7.8.2.1 Diagnosis vs Signs and Symptoms

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

7.8.2.2 Deaths

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

7.8.2.3 Preexisting Medical Conditions

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

7.8.2.4 Hospitalizations for Medical or Surgical Procedures

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

- Hospitalizations for the following reasons do not require reporting:
- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

7.8.2.5 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.03. will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

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

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

Note: Based on the most recent version of NCI CTCAE v4.03 which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

7.8.2.6 Pregnancy

A report should be completed and expeditiously submitted to Genentech, Inc under the following circumstances:

- If a female subject becomes pregnant while receiving the study drug or within 18 months after the last dose of study drug
- 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 study drug

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 drug should be reported as an SAE.

7.8.2.7 Post – Study Adverse Events

For studies involving collection of survival data/ 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 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 during this period to ensure successful transmission of Single case reports.

7.8.2.8 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 lead study staff emailing Genentech a Quarterly line-listing documenting single case reports sent by the lead site 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 the lead site 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

7.8.2.9 AEs of Special Interest

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

The Obinutuzumab Events of Special Interest are:

- Tumor lysis syndrome (irrespective of seriousness, causality or severity)
- Second malignancy

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

7.8.2.10 Exchange of Single Case Reports

The lead site study team will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

Investigators must report all the above mentioned single case reports adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at

the following contacts:

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

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

All Product Complaints without an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

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

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), and other Special Situation Reports where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

SADRs

- Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

Other SAEs

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

AESIs

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

Special Situation Reports

- **Pregnancy reports**

While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the

partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

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

Other Special Situation Reports

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

Data related to the Product usage during breastfeeding

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

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

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

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

Follow-Up Information

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

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

7.8.3 Reporting to Regulatory Authorities, Ethics Committees and Investigators

The lead site, 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.

The lead site, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

The lead site will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

The lead site 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 (if applicable):

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

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

7 Calendar Day Telephone or Fax Report:

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

15 Calendar Day Written Report

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

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR

§ 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

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

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

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

Genentech Drug Safety:

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

The lead site/ Overall PI will be responsible for the distribution of safety information to its own investigators, where relevant.

The lead site will be responsible for the distribution of safety information to the site IRB as applicable.

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

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

7.8.4 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 mail box: ctvist_drugsafety@gene.com

7.8.5 Final Study Report

The lead site/Overall PI will forward a copy of the Final Study Report to Genentech upon completion of the study.

7.8.6 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:

Clinical Ops mailbox: ga101-gsur@gene.com and to Genentech Safety CTV oversight mailbox at: ctvist_drugsafety@gene.com

7.8.7 Queries

Queries related to the Study will be answered by lead site/ Overall PI. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to obinutuzumab. The Overall PI/Lead site shall not answer such queries from regulatory authorities and other sources relating to obinutuzumab independently but shall redirect such queries to Genentech.

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

7.8.8 Safety Crisis Management

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

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

7.8.8.1

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the agents administered in this

study can be found in Section 7.1.

8.1 Ibrutinib

8.1.1 Description

The chemical name is: 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one. Ibrutinib is also known as PCI-32765. The molecular formula is C₂₅H₂₄N₆O₂. The molecular weight is 440.5 g/mol. 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. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

Mean peak plasma concentrations are observed between 1 and 2 hours after dosing, and drug exposure increases in a dose-dependent fashion. The half-life of the drug ranges from 4 to 8 hours

8.1.2 Dose and Administration

Ibrutinib 420 mg (3 x 140-mg 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 capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. Ibrutinib may be administered without regard to meals. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study.

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

The first dose will be given in the clinic by the treatment nurse, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be supplied to patients from Biologics Oncology Pharmacy. Patients will be asked to bring their ibrutinib supply to clinic on Cycle 1 Day 1 for the first dose administration. Drug bottles are to be destroyed by the patient per instructions from Biologics Oncology Pharmacy.

8.1.3 Form

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. Refer to the ibrutinib Investigator's 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 drug will be dispensed in child-resistant packaging.

Refer to the package insert for additional guidance on study drug storage, preparation and handling.

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

8.1.4 Storage and Stability

The recommended storage condition for ibrutinib capsules is room temperature (15 to 25°C; 59 to 77°F). Refer to the package insert for additional guidance on study drug preparation and handling.

8.1.5 Compatibility

Not applicable

8.1.6 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agents in a self-contained and protective environment.

Caution is required when handling ibrutinib. Pharmacists should follow standard procedures for the handling of investigational drugs, including avoidance of eye or skin contact with the drug product. If there is exposure to the drug product, provide treatment as necessary for physical exposure (skin washing) or inhalation (move to fresh air) and seek medical advice as necessary.

When ibrutinib capsules are distributed for self-administration, they should only be handled by the study subject. After handling capsules, the subject should wash their hands thoroughly. If someone who is not enrolled in a clinical trial involving ibrutinib swallows a capsule or inhales drug powder from a broken capsule of ibrutinib, they should contact the relevant Principal Investigator to determine whether safety monitoring is necessary. Capsules should always be stored in the container provided to the study subject.

8.1.7 Availability

Ibrutinib is an FDA-approved drug that is manufactured by Pharmacyclics, Inc., Sunnyvale, CA, and will be given through commercial supply on this study.

8.1.8 Preparation

Ibrutinib comes in capsule form, and final packaging and labeling are done commercially.

8.1.9 Administration

Ibrutinib is self-administered orally as a capsule formulation daily in 28 day cycles as a fixed dose of 420 mg, and should be administered using the minimal number of capsules necessary. Doses must be taken every 24 hours as close to the same time each day. The date, time, and quantity of each capsule strength taken will be recorded in a drug self-administration diary. Patients should record any deviation from taking the full daily dose (e.g., vomited doses, missed doses, doses reduced due to missing or lost capsules). An attempt should be made to enable each dose to be taken at approximately the same time of day. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day, with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose. Vomited doses should not be taken or repeated. Ibrutinib capsules should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL) at approximately the same time(s) each day. Ibrutinib may be administered without regard to meals. Patients must avoid Seville oranges and grapefruit or grapefruit juice.

8.1.10 Ordering

Ibrutinib on this study will come from commercial supply, and patients will obtain the drug as per standard of care.

Drug may be shipped per institutional policy to the patient if necessary, and does not warrant specific or individual approval from the Overall Principal Investigator.

8.1.11 Accountability

Patients will be responsible for the accountability of ibrutinib on this study through the drug self-administration diary, since the drug is being obtained from commercial supply.

8.1.12 Destruction and Return

As ibrutinib is being provided through commercial supply, patients will be responsible for properly destroying all unused ibrutinib appropriately as per standard guidelines.

8.1.13 Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose. There is no specific antidote for ibrutinib. In the event of an

overdose, subjects should be closely monitored and given appropriate supportive treatment.

Refer to Section 11 for further information regarding AE reporting,

8.2 Obinutuzumab

8.2.1 Formulation

Obinutuzumab is provided as a single-use vial. 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 25 mg/mL drug substance formulated in histidine/histidine-HCl, trehalose, and poloxamer 188. The vial contains 41 mL (with 2.5% overfill).

8.2.2 Ordering

Each participating site will be provided with a study specific order form provided by Genentech once all required documentation of DFCI approval has been supplied to Genentech by the lead site.

8.2.3 Storage

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 24 hours 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 aseptic 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.

Preparation

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

One vial may be used to prepare both the 100-mg dose (equals 4 mL) and 900-mg dose (equals 36 mL) following the directions below. If both bags are prepared at the same time, the reconstitution/dilution has to take place in a controlled and validated aseptic conditions. Subsequently store the 900-mg bag for a maximum of 24 hours at 2°C – 8°C and administer the next day.

To prepare a 100-mg dose: The final drug concentration of a 100-mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl,

withdraw and discard 4 mL of the sodium chloride. Withdraw 4 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 900-mg dose: The final drug concentration of a 900-mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 36 mL of the sodium chloride. Withdraw 36 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 1000-mg dose: The final drug concentration of a 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 it 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 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.

8.2.4 Dosage and Administration

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

- On first cycle, Day 1, 100 mg obinutuzumab will be administered
- On first cycle, Day 2, 900 mg of obinutuzumab will be administered
- On first cycle, Days 8 and 15, 1000 mg of obinutuzumab will be administered.
- On cycles 2-6, Day 1, 1000 mg of obinutuzumab will be administered (see table 4)

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision by the investigator at all times. Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps (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.

8.2.4.1 Premedication Requirements

Infusion-Related Reactions

Since some patients may develop hypersensitivity or other IRRs to obinutuzumab, the following pre-medication is recommended to reduce the risk of infusion reactions as outlined below. Sites may also administer pre-medications according to their local standard of care for obinutuzumab:

- Cycle 1, Days 1 and 2, all patients require pre-medication with:
 - IV glucocorticoid: methylprednisolone (80 mg) 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.
 - An oral acetaminophen (1000 mg) and an IV antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each obinutuzumab infusion.
- Cycle 1, Days 8 and 15 and Cycles 2-6, Day 1:
 - All patients require pre-medication with oral acetaminophen (1000 mg) 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 (50 mg) administered at least 30 minutes before starting each subsequent obinutuzumab infusion.
 - Patients who experience a Grade 3 IRR with the previous infusion or who have lymphocyte counts of $\geq 25 \times 10^9/L$ prior to the next treatment will require pre-medication with IV glucocorticoid: methylprednisolone (80 mg) 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 treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their hypertensive medication.

For TLS prophylaxis, see Section 5.5.2.

8.2.4.2 Obinutuzumab Dosing

The first 1000 mg of obinutuzumab will be administered over 2 days. During Cycle 1, Day 1, 100 mg will be administered. On the following day (Cycle 1, Day 2), 900 mg will be administered (see Table 4).

Table 4 Obinutuzumab Dosing Schedule

Cycle and Day of Administration		Dose of Obinutuzumab	Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)
Cycle 1	Day 1	100 mg	Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hour. The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.
	Day 15	1000 mg	
Cycles 2–6	Day 1	1000 mg	

8.2.5 Dosage Modification/Toxicity Management

If a patient experiences an IRR during infusion, adjust the infusion as follows:

- Grade 4 (life-threatening): Stop infusion immediately and discontinue obinutuzumab therapy.
- 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.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Laboratory Correlative Studies

9.1.1 BH3 Profiling

BH3 profiling is a functional assay we previously developed that detects the proximity of CLL cells to the threshold of apoptosis (what we call ‘priming’) through interrogation of BCL-2 family members. To perform a BH3 profile, we add individual BH3-only peptides to gently permeabilized malignant cells and use FACS to measure the amount of mitochondrial depolarization induced by each peptide, as measured by cytochrome c release.

We hypothesize that patients whose cells undergo significant depolarization to BIM BH3 peptide (highly primed) will have superior clinical response to ibrutinib plus obinutuzumab compared to patients whose cells undergo minimal BIM BH3 depolarization (unprimed). These assessments will be made on circulating CLL cells from the peripheral blood drawn from patients at baseline.

If we have bone marrow aspirates and fresh lymph node tissue available, we will also perform BH3 profiling to see whether the level of priming in CLL cells from these tissues is a better predictor of response than peripheral blood CLL cells.

After 1 week of combination therapy, we will obtain another peripheral blood sample. We will compare the BH3 profile of this steady-state sample to a baseline sample, which will allow us to assess *in vivo* the short term change in apoptotic priming induced by ibrutinib given in combination with obinutuzumab. We will also attempt to identify potential resistance mechanisms by looking at whether patients who do not achieve CR have different upfront BH3 profiles from those who do. Finally, another sample of peripheral blood will be collected from subjects at the time of disease progression, and the BH3 profile of these samples will be compared to subjects’ baseline samples to help identify whether a change in anti-apoptotic protein dependence is observed as a possible mechanism of resistance.

All peripheral blood samples will promptly be delivered to the laboratory of Dr. Jennifer Brown where they will undergo Ficoll purification and then be viably frozen in FBS with 10% DMSO. The viably-frozen samples will be batched and later transported to the laboratory of Dr. Anthony Letai, where the BH3 profiling assays will be performed (for detailed methods see Ryan et al., 2010).

9.1.2 Genomic Analysis

We plan to perform whole exome sequencing on CLL cells and normal tissue from patients at baseline to evaluate for somatic mutations such as *NOTCH1* and *SF3B1* that may confer drug sensitivity and resistance. If the patient does not have significant circulating CLL cells, bone marrow aspirate should be obtained as well in patients who require a new bone marrow biopsy for screening. In addition, saliva as a source of germline will be collected prior to study initiation and may be collected more than once if inadequate specimen is obtained. All samples

will promptly be delivered to the laboratory of Dr. Jennifer Brown, where DNA will be extracted and then sent to the Broad Institute (Cambridge, MA) for whole exome sequencing. In an exploratory analysis, we will assess novel mutations as potential predictors of response and progression-free survival. We will also collect a sample from each patient at time of relapse or progression for repeat analysis by whole exome sequencing to assess for acquired resistance mutations.

9.1.3 Sequenta Sequencing Studies

The following samples will be collected and stored in the laboratory of Dr. Jennifer Brown at Dana-Farber Cancer Institute for possible future analysis. Further information regarding sample analysis is outlined below.

Peripheral blood and/or bone marrow samples may be collected for analysis both at a pretreatment visit and at the re-staging evaluation at the conclusion of the combination portion of the study. Using Sequenta's LymphoSIGHT platform, rearranged immunoreceptor loci from genomic DNA will be extracted, amplified, and sequenced using V and J segment primers for each immunoreceptor gene. Tumor-specific clonotypes will be identified for each patient based on their high prevalence in peripheral blood or bone marrow. Sequences will be analyzed using standardized algorithms for clonotype determination. Sequenta MRD levels will be quantified using spiked-in reference sequences.

9.1.4 Genzyme Minimal Residual Disease and Additional Prognostic Tests

Bone marrow samples will be collected for minimal residual disease analysis by Genzyme Genetics by flow cytometry at the end of combination therapy and again approximately 12 months after combination therapy in patients who remain in CR. Patients who have not already had ZAP-70, *TP53* and *IGHV* testing will send additional baseline samples to Genzyme/LabCorp. These samples will be shipped alongside the Integrated Oncology/LabCorp requisition form ambient priority overnight to:

Genzyme/LabCorp Specialty Testing Group
521 West 57th Street
New York, NY 10000

9.1.5 Sample Collection Schedule

Sample Time Point	Container ¹	Sample Type ²	Shipping Method	Recipient ⁴
Screening or Pre-dose Day 1	1 x 6 mL Green Top 1 x 3 mL Purple Top	Bone Marrow Aspirate	Fridge pack overnight	CLL Center, J. Brown lab
	6 x 6 mL Green Top 1 x 6 mL Red Top 1 x 10mL Purple Top	Peripheral Blood		
	1 x Oragene Kit	Saliva ³	Ambient overnight	Genzyme/LabCorp
	2 x 10 mL Purple 1 x 6 mL Green Top*	Peripheral Blood	Fridge pack overnight	
After 1 week of combination therapy	6 x 6 ml Green Top 1 x 6 mL Red	Peripheral Blood	Fridge pack overnight	CLL Center J. Brown lab
End of Combination Therapy ²	1 x 6 mL Green Top 1 x 3mL Purple Top	Bone Marrow Aspirate	Fridge pack overnight	CLL Center, J. Brown lab
	6 x 6 mL Green Top 1 x 6 mL Red Top 1 x 10 mL Purple Top	Peripheral Blood		
	2 x 6 mL Green Top ⁵	Peripheral Blood	Fridge pack overnight	Genzyme/LabCorp
	1 x 6 mL Green Top ⁵	Bone Marrow Aspirate		
Every 6 months from C7D1 ^{6,8}	6 x 6 mL Green Top 1 x 6 mL Red Top	Peripheral Blood	Fridge Pack overnight	CLL Center, J. Brown lab
12 months after Combination Therapy	6x6mL Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
	1x6ml Green top	Bone Marrow Aspirate		
	1x6ml Green Top ^{5,7}	Bone Marrow Aspirate	Fridge pack overnight	Genzyme/LabCorp
Relapse/Disease Progression	1 x 6 mL Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
	6 x 6 mL Green Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
	1 x 6 mL Green Top	Bone Marrow Aspirate		

¹ Green top= sodium heparin tube; Red top= no additive; Purple top: K2EDTA

²For time points that mention blood and or aspirate: If patient has few circulating CLL cells in peripheral blood, send additional aspirate (1 x 6 mL green top tube) in addition to blood

³Oragene kits will be provided by the lead site, and requires approximately 2 mLs of saliva

⁴Genzyme/LabCorp only provides requisition form

⁵For MRD analysis

⁶Requested for all patients who remain on study; ie: stable disease to morphologic/radiographic CR

⁷ Bone marrow biopsy required every 12 months from C19D1 for patients who are not MRD negative, otherwise not needed

⁸every 6 months from C7D1 for Arms A+C, and every 6 months from C13D1 for Arm B

⁹ Unless unavoidable, for timepoints where both blood and aspirate are requested, both should be drawn on the same day

* Samples required for all patients at baseline unless previously tested for ZAP-70, *IGHV* and *TP53* testing.

Marrow timing may vary depending on arm patients are randomized- See Section 10 study calendars for reference

****Samples must be couriered Monday through Thursday only and delivered preferably within 24 hours of draw time.**

Screening dates (dates where baseline blood and aspirate are drawn) will need to be discussed and approved by the lead site prior to shipment.

All samples must be sent to the address listed below. An email should also be sent to the lead site coordinator and the lab technician as soon feasible notifying them of an incoming sample. The email should include the Fed Ex tracking number of the shipment, the completed sample requisition form and any other information deemed pertinent.

Stacey Fernandes, Principal Research Technician
CLL Center, J. Brown lab
Dana Farber Cancer Institute
1 Jimmy Fund Way, JFB 426
Boston, MA 02115, U.S.A.
617-632-5828 (phone)

Correlative studies note: While the goal of the correlative studies is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, not perform, or discontinue an analysis due to either practical reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc). Therefore, depending on the results obtained during the study, sample collection/analysis may be omitted at the discretion of the PI.

10. STUDY CALENDAR

Baseline evaluations are to be conducted 30 days or less prior to registration unless otherwise indicated. Baseline laboratory testing should be completed within 2 weeks of registration unless otherwise indicated. If a participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to starting the next therapy cycle.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date during the initial monotherapy and combination portions of the study and ± 7 days after combination therapy is completed, unless otherwise noted.

After cycle 37, participants may return to the main research site every 6 cycles (168 days $\pm$ 14 days) if they are being followed by a local hematologist/oncologist in the interim q3 cycles (84 $\pm$ 14 days). No study specific assessments need occur at the interim visits. Those who remain at the main research institution for all visits will continue to be seen every 3 cycles.

- Cycles 10-37 (every 84 days $\pm$ 14 days) **OR** Cycle 10-Onward (every 84 days $\pm$ 14 days) for those not being followed by a local hematologist/oncologist:
 - Medical history, physical exam, vital signs (pulse, BP, temperature), PS, AEs, concomitant medication
 - Serum chemistry, hematology
 - SPEP only if M protein detected at baseline (every 6 cycles)
 - IgA, IgM, IgG if no M-Protein detected at baseline (every 6 cycles)
 - Correlative sample collection every 6 cycles after C1D1
 - Bone marrow biopsy/aspirate and scans at investigator's discretion after Cycle 37
- After the cycle 37 visit, patients will have the option of being seen every other visit (approximately every 6 cycles or 168 $\pm$ 14 days) by a hematologist/oncologist locally instead of q3 month visits at the main research institution to reduce travel burden. For patients who elect to do this, the following will should occur at their local provider's office:
 - Standard of care comprehensive blood count with differential and a comprehensive chemistry panel should be completed
 - Adverse Event assessment will be done over the phone or by email between the patient and the main research nurse/investigator and documented in the EMR/study chart.
 - For the visits that occur at the main research institution, assessments described above (Cycles 10-onward)

Arm A

<i>Cycle = 28 days</i>	Screening	Cycle 1 (+-3 Days)				Cycle 2 (+-3 Days)				Cycles 3-6 (+-3 Days)	Cycle 7 (+-3 days)	Cycles 10+ (Every 3 cycles ¹⁴)	Cycle 13 ¹⁴	Follow Up (every 3 cycles until new therapy, death, or withdrawal)	Disease Progression/ End of Treatment ⁸
Procedure	Day -30 to 0	Day 1	Day 2	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Day 1	Day 1		
Obinutuzumab		X	X	X	X	X				X					
Ibrutinib		Daily Dosing - Days 1 – 28													
Informed consent	X														
Survival Status ¹³														X	
Medical history	X	X		X	X	X	X	X	X	X	X	X	X		X
Physical examination	X	X		X	X	X	X	X	X	X	X	X	X		X
Serum Pregnancy test	X														
Vital signs (height, weight, respiratory rate, pulse rate, BP, temp, O ₂ sat)	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urinalysis	X														
BM aspirate/biopsy/MRD assessment ^{1, 2, 3}	X ³									X ³	X ²				X ^{2,3}
SPEP + Immunoglobulins ⁴	X									X		X	X		
ECOG performance status	X	X		X	X	X	X	X	X	X	X	X	X		
EKG	X														
Serology: HIV, HCV, HBV	X														
CT scan (+/- 7 days)	X									X ⁵	X ⁵		X ^{5,6}	X ^{5,6}	X
Hematology ⁹	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Serum Chemistry ¹⁰	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PT/PTT/INR	X														
FISH Analysis ¹¹	X														
IGHV, TP53, ZAP-70, NOTCH1 ¹²	X														
Correlative studies	X ^{7,3}	X					X				X				X ³
Adverse Event Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X		X

¹ Unilateral bone marrow aspirate and/or biopsy required within 90 days prior to Day 1 of Cycle 1

² MRD assessment should be sent on marrow and blood 28 days after last dose of obinutuzumab (+/-7days)

³ Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care, or as part of protocol schedule. Flow cytometry (lymphoma panel), karyotype, and FISH (CLL) should be performed on marrow at all bone marrow biopsies (FISH may be performed on either marrow or blood and is not required on both)

⁴ SPEP at baseline and every 3 cycles thereafter only if M protein detected at baseline; if no M protein detected at baseline, IgG, IgA, IgM to be checked every 3 months. After Cycle 37, both SPEP and Immunoglobulin assessments will be performed every 6 cycles in participants where they apply.

⁵ Just prior to cycles 3, 7, and 13 (Chest, Abdomen, Pelvis and Neck- Neck is required only if there is palpable cervical lymphadenopathy at baseline)

⁶ After Month 12, CT scans will occur at minimum every 6 months (+/- 2 weeks) or at a shorter interval until Cycle 37 and beyond, where scans may then be done at the investigator's discretion

⁷ Baseline correlative studies may be obtained either at the screening visit or prior to study drug administration on C1D1.

⁸ End of treatment should be completed within 30 days of last dose of study treatment

¹⁰ Calcium, Sodium, Potassium, Phosphorus, Chloride, Glucose, Magnesium, Albumin, AST, ALT, Creatinine, BUN, Bicarbonate, Total protein, Total bilirubin (and direct bilirubin if total Bilirubin is abnormal), Uric acid, LDH, Alkaline phosphatase. Lipase, Amylase, and beta-2 M are required at baseline

¹¹ Performed on either marrow or peripheral blood within 6 months prior to C1D1.

¹² Collected at screening unless previously tested for.

¹³ Survival data may be collected by phone if necessary

¹⁴ After cycle 37, participants may return to the main study site every 6 cycles (168 days+/-14 days) if they are being followed by a local hematologist/oncologist in the interim q3 cycles (84 +/-14 days). No study specific assessments need occur at the interim visits. Those who remain at the main research institution for all visits will continue to be seen every 3 cycles. Please refer to the beginning of Section 10 for additional details.

Arm B

¹ Unilateral bone marrow aspirate and/or biopsy required within 90 days prior to Day 1 of Cycle 1

² MRD assessment should be sent on marrow and blood 28 days after last dose of obinutuzumab (+/-7days)

<i>Cycle = 28 days</i>	Screening	Cycle 1 (+3 Days)		Cycle 2 (+3 Days)					Cycles 3-6 (+ 3 Days)	Cycle 7 (+ 3 Days)	Cycle 8 (+ 3 days)	Cycles 10+ (Every 3 cycles) ¹⁴	Cycle 13¹⁴	Follow Up (every 3 cycles until new therapy, death, or withdrawal)	Disease Progression/ End of Treatment⁸
Procedure	Day -30 to 0	Day 1	Day 8	Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 1	Day 1	Day 1	Day 1		
Obinutuzumab				X	X	X	X		X	X					
Ibrutinib		Daily Dosing - Days 1 – 28													
Informed consent	X														
Survival Status ¹²														X	
Medical history	X	X	X	X		X	X	X	X	X	X	X	X		X
Physical examination	X	X	X	X		X	X	X	X	X	X	X	X		X
Serum Pregnancy test	X														
Vital signs (height, weight, respiratory rate, pulse, BP, temp, O ₂ sat)	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urinalysis	X														
BM aspirate / biopsy / MRD assessment ^{1, 2, 3}	X ³								X ³		X ²				X ^{2,3}
SPEP + Immunoglobulins ⁴	X								X			X	X		
ECOG performance status	X	X	X	X		X	X	X	X	X	X	X	X		
EKG	X														
Serology: HIV, HCV, HBV	X														
CT scan (+/- 7 days)	X								X ⁵		X ⁵		X ^{5,6}	X ^{5,6}	X
Hematology ⁹	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Serum Chemistry ¹⁰	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PT/PTT/INR	X														
FISH Analysis ¹¹	X														
IGHV, TP53, ZAP-70, NOTCH1 ¹²	X														
Correlative studies	X ^{7,3}	X				X					X				X ³
Adverse Event Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X		X

³ Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care, or as part of protocol schedule. Flow cytometry (lymphoma panel), karyotype, and FISH (CLL) should be

performed on marrow at all bone marrow biopsies (FISH may be performed on either marrow or blood and is not required on both)

⁴ SPEP at baseline and every 3 cycles thereafter only if M protein detected at baseline; If no M protein detected at baseline, IgG, IgA, IgM to be checked every 3 months. After Cycle 37, both SPEP and Immunoglobulin assessments will be performed every 6 cycles in participants where they apply.

⁵ Just prior to cycles 3, 8, and 13 (Chest, Abdomen, Pelvis and Neck- Neck is required only if there is palpable cervical lymphadenopathy at baseline)

⁶ After Month 12, CT scans will occur at minimum every 6 months (+/- 2 weeks) or at a shorter interval until Cycle 37 and beyond, where scans may then be done at the investigator's discretion

⁷ Baseline correlative studies may be obtained either at the screening visit or prior to study drug administration on C1D1

⁸ End of treatment should be completed within 30 days of last dose of study treatment

⁹ CBC w/ differential, hemoglobin, hematocrit, platelets

¹⁰ Calcium, Sodium, Potassium, Phosphorus, Chloride, Glucose, Magnesium, Albumin, AST, ALT, Creatinine, BUN, Bicarbonate, Total protein, Total bilirubin (and direct bilirubin if total Bilirubin is abnormal), Uric acid, LDH, Alkaline phosphatase. Lipase, Amylase, and beta-2 M are required at baseline

¹¹ Performed on either marrow or peripheral blood within 6 months prior to C1D1¹² Collected at screening unless previously tested for.

¹² Survival data may be collected by phone if necessary

¹³ After cycle 37, participants may return to the main study site every 6 cycles (168 days+/-14 days) if they are being followed by a local hematologist/oncologist in the interim q3 cycles (84 +/-14 days). No study specific assessments need occur at the interim visits. Those who remain at the main research institution for all visits will continue to be seen every 3 cycles. Please refer to the beginning of Section 10 for additional details and requirements.

ARM C

<i>Cycle = 28 days</i>	Screening	Cycle 1 (+-3 Days)					Cycle 2 (+-3 Days)		Cycles 3-6 (+-3 Days)	Cycle 7 (+-3 days)	Cycles 10+ (Every 3 cycles) ¹⁴	Cycle 13 ¹⁴	Follow Up (every 3 cycles until new therapy, death, or withdrawal)	Disease Progression/End of Treatment ⁸
Procedure	Day -30 to 0	Day 1	Day 2	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1		
Obinutuzumab		X	X	X	X		X		X					
Ibrutinib		Daily Dosing - Days 1 – 28												
Informed consent	X													
Survival Status ¹³													X	
Medical history	X	X		X	X	X	X	X	X	X	X	X		X
Physical examination	X	X		X	X	X	X	X	X	X	X	X		X
Serum Pregnancy test	X													
Vital signs (height, weight, respiratory rate, pulse rate, BP, temp, O ₂ sat)	X	X	X	X	X	X	X	X	X	X	X	X		X
Urinalysis	X													
BM aspirate / biopsy/ MRD assessment ^{1, 2, 3}	X ³								X ³	X ²				X ^{2,3}
SPEP + Immunoglobulins ⁴	X								X		X	X		
ECOG performance status	X	X		X	X	X	X	X	X	X	X	X		
EKG	X													
Serology: HIV, HCV, HBV	X													
CT scan (+/- 7 days)	X								X ⁵	X ⁵		X ^{5,6}	X ^{5,6}	X
Hematology ⁹	X	X	X	X	X	X	X	X	X	X	X	X		X
Serum Chemistry ¹⁰	X	X	X	X	X	X	X	X	X	X	X	X		X
PT/PTT/INR	X													
FISH Analysis ¹¹	X													
IGHV, TP53, ZAP-70, NOTCH1 ¹²	X													
Correlative studies	X ^{7,3}	X		X						X				X ³
Adverse Event Evaluation	X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X		X

¹ Unilateral bone marrow aspirate and/or biopsy required within 90 days prior to Day 1 of Cycle 1

² MRD assessment should be sent on marrow and blood 28 days after last dose of obinutuzumab (+/-7days)

³ Marrow sample requested for correlative studies if bone marrow biopsy is done as standard of care, or as part of protocol schedule. Flow cytometry (lymphoma panel), karyotype, and FISH (CLL) should be performed on marrow at all bone marrow biopsies (FISH may be performed on either marrow or blood and is not required on both)

⁴ SPEP at baseline and every 3 cycles thereafter only if M protein detected at baseline; If no M protein detected at baseline, IgG, IgA, IgM to be checked every 3 months- After Cycle 37, both SPEP and Immunoglobulin assessments will be performed every 6 cycles in participants where they apply.

⁵ Just prior to cycles 3, 7, and 13 (Chest, Abdomen, Pelvis and Neck- Neck is required only if there is palpable cervical lymphadenopathy at baseline)

⁶ After Month 12, CT scans will occur at minimum every 6 months (+/- 2 weeks) or at a shorter interval until Cycle 37 and beyond, where scans may then be done at the investigator's discretion

⁷ Baseline correlative studies may be obtained either at the screening visit or prior to study drug administration on C1D1

⁸ End of treatment should be completed within 30 days of last dose of study treatment

⁹ CBC w/ differential, hemoglobin, hematocrit, platelets

¹⁰ Calcium, Sodium, Potassium, Phosphorus, Chloride, Glucose, Magnesium, Albumin, AST, ALT, Creatinine, BUN, Bicarbonate, Total protein, Total bilirubin (and direct bilirubin if total Bilirubin is abnormal), Uric acid, LDH, Alkaline phosphatase. Lipase, Amylase, and beta-2 M are required at baseline

¹¹ Performed on either marrow or peripheral blood within 6 months prior to C1D1.

¹² Collected at screening unless previously tested for

¹³ Survival data may be collected by phone if necessary

¹⁴ After cycle 37, participants may return to the main study site every 6 cycles (168 days+/-14 days) if they are being followed by a local hematologist/oncologist in the interim q3 cycles (84 +/-14 days). No study specific assessments need occur at the interim visits. Those who remain at the main research institution for all visits will continue to be seen every 3 cycles. Please refer to the beginning of Section 10 for additional details and requirements.

11. MEASUREMENT OF EFFECT

11.1 Definitions

Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response: Only those participants who have received at least one cycle of combination therapy and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

11.2 Methods for Evaluation of Measurable Disease

All lymph node measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations (physical exam and radiographic evaluations) should be performed as closely as possible to the beginning of treatment and not more than 30 days prior to registration.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

11.3 Response Criteria

Response and progression will be evaluated in this study using the 2008 IW-CLL criteria for CLL (Hallek et al., 2008)

11.3.1 Complete remission (CR):

CR requires all of the following criteria:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below $4 \times 10^9/L$ ($4000/\mu L$). The presence of minimal residual disease (MRD) after therapy should be assessed. The sensitivity of the method used to evaluate for MRD should be reported.

- Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical examination. A CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.
- No hepatomegaly or splenomegaly by physical examination. A CT scan of the abdomen should be performed at response assessment if found to be abnormal before therapy or if physical examination is inconclusive at the time of evaluation.
- Absence of constitutional symptoms.
- Blood counts above the following values: Neutrophils more than $1.5 \times 10^9/L$ (1,500/ μL) without need for exogenous growth factors, Platelets more than $100 \times 10^9/L$ (100,000/ μL) without need for exogenous growth factors, Hemoglobin more than 110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin.
- Bone marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent.

11.3.2 Complete remission with incomplete marrow recovery (CRi):

Patients who fulfill all the criteria for a CR but who have a persistent anemia or thrombocytopenia or neutropenia felt unrelated to CLL but related to drug toxicity. Bone marrow examination must reveal no clonal B-cell population by flow cytometry.

11.3.3 Minimal Residual Disease

Patients who achieve CR or CRi will be assessed for minimal residual disease (MRD). Such patients who have fewer than 0.01% (10^{-4}) CLL cell percentage of leukocytes in the bone marrow, as assessed by four-color flow cytometry, will be considered to be MRD-negative.

11.3.4 Partial Response (PR)

- A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.
- Reduction in lymphadenopathy as defined by the following:
 - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy.
 - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.
- A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more
- The blood count should show one of the following results: Neutrophils more than $1.5 \times 10^9/L$ (1,500/ μL) without need for exogenous growth factors, Platelet counts greater than $100 \times 10^9/L$ (100,000/ μL) or 50% improvement over baseline without need for exogenous growth factors, Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

11.3.5 Partial Response with lymphocytosis (PR-L)

It is anticipated some patients will experience increased lymphocytosis after starting ibrutinib and may not fully clear the lymphocytosis with the addition of obinutuzumab. This is a well-

known phenomenon that is a class effect of the BCR inhibitor drugs. In clinical experience, these patients appear to derive a similar clinical benefit from BCR inhibitors as patients who achieve a traditional PR. Therefore, a revision to the IWCLL criteria was proposed and is now widely recognized. As per Cheson et al., 2012, patients who achieve a radiographic PR but continue to have a lymphocytosis with $>5,000$ B-lymphocytes per μL where the absolute lymphocyte count has not decreased by 50% or more compared to baseline are considered to have PR with lymphocytosis, also known as a nodal partial response.

11.3.6 Nodular Partial Response (nPR)

All criteria for CR are met, but lymphoid nodules can be found in the bone marrow biopsy. Note, if flow cytometry and immunohistochemistry are negative for a clonal B-cell population then these patients can be considered as CR or CRi.

11.3.7 Progressive disease (PD)

Progressive disease during or after therapy is characterized by at least one of the following:

- Lymphadenopathy. Progression of lymphadenopathy is often discovered by physical examination and should be recorded. For CT scans used to confirm progression or relapse of lymphadenopathy, progression is defined as:
 - An increase by 50% or more in greatest determined diameter of any previous site.
 - An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
 - An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per microliter (*Note*: because of the well-described lymphocyte redistribution phenomenon, any increase in lymphocyte count during ibrutinib monotherapy or any increase during combination therapy in the setting of improvement of lymph nodes or cytopenias will not be considered disease progression)
 - Transformation to a more aggressive histology (eg, Richter syndrome). This diagnosis must be established by lymph node biopsy.
 - Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) due to CLL.
- During therapy, cytopenias cannot be used to define disease progression.
- After therapy, the progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than $100 \times 10^9/\text{L}$ ($100,000/\mu\text{L}$), which occurs at least 3 months after treatment, defines disease progression, if marrow biopsy demonstrates an infiltrate of clonal CLL cells.

11.3.8 Stable disease (SD)

Patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease.

11.3.9 Treatment failure

Responses that should be considered clinically beneficial include CR and PR; all others (eg,

stable disease, non-response, progressive disease, or death from any cause) should be rated as a treatment failure.

11.3.10 Time to progression, progression-free survival, and overall survival

Time to progression (TTP) is defined as the time from study entry until objective disease progression. Progression-free survival (PFS) is defined as the time from study entry until objective disease progression or death. Overall survival is defined as the time from study entry until death from any cause.

11.4 Response Review

Radiology will be centrally reviewed by the DF/HCC Tumor Imaging Metrics Core (TIMC)

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary objective of this phase Ib study of obinutuzumab in combination with ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia is to determine the optimal treatment schedule of obinutuzumab and ibrutinib. The primary endpoint is safety and a two-stage design will be employed to test the safety of three combination schedules of obinutuzumab and ibrutinib: Arm A (obinutuzumab alone for 1 cycle followed by the combination of obinutuzumab and ibrutinib), Arm B (ibrutinib alone for 1 cycle followed by the combination of obinutuzumab and ibrutinib), Arm C (ibrutinib and obinutuzumab started simultaneously in cycle 1).

In the first stage, 30 patients will be randomly allocated to Arm A, B, or C in 1:1:1 using a permuted block algorithm within strata. In the first 10 patients in each arm, if 3 or more patients experience DLT, this arm will be terminated after the first stage and removed from further consideration. If 3 or more DLTs seen in the first stage in all 3 arms, the study will be terminated early. If 2 or fewer patients experience DLT, this arm will be moved to the second stage enrolling 10 additional patients. If no DLTs are seen in any arm, we plan to use other metrics to determine which of the two Arms to expand. These metrics may include, incidence of infusion reactions, overall tolerability, and consideration of other important medical events. If two or more arms move to the second stage, additional patients will be randomly allocated to each arm in a 1:1 ratio with 10 patients per arm. After the second stage, if 4 or fewer patients in 20 experience DLT, this schedule will be regarded as safe for a future study. After the second stage, if one or more arms are regarded as safe, we will consider other factors such as toxicity profile, particularly SAEs, efficacy profile, and/or results from correlative studies to determine the best treatment schedule for a future study. If two or more arms are completely matched in the end in terms of both safety and efficacy then we would choose the arm that is most convenient schedule-wise for a future study.

With this design, the probability of early termination after the first stage will be 0.07 if the true but unknown DLT rate is 10%, but 0.74 if the rate is 35%. After the completion of the second stage, the probability of regarding an arm as safe is 0.91 if the true but unknown DLT rate is 10% but 0.09 if the rate is 35%. Table 5 below presents the operating characteristics of this design.

Table 5. Operating Characteristics

	True but unknown rate of DLT						
	0.05	0.1	0.15	0.2	0.25	0.3	0.35
Prob. of Stopping early (>2 in the first 10)	0.01	0.07	0.18	0.32	0.47	0.62	0.74
Prob. of a treatment schedule safe (<=2 in first 10 and <=4 in 20)	0.99	0.91	0.75	0.54	0.35	0.19	0.09

January 8th, 2018

The study has completed the first stage by accruing 10 patients to each of the three arms. None of the arms have met the stopping rule of 3 or more DLTs in the first 10 patients. However, Arm A has a very high infusion reaction rate to obinutuzumab (5/10) compared to Arm B (1/10) and C (0/10). Although none of the infusion reactions in Arm A were severe enough to be formally considered DLTs, this treatment schedule (Arm A) is ruled out for consideration of the optimal treatment schedule due to excessive infusion reactions, and will be closed to further accrual. The study will expand Arms B and C to accrue 10 additional patients each as per protocol and all future patients will be randomized 1:1 between Arms B and C.

13.2 Sample Size and Accrual

The sample size will range approximately from 9-60 patients, depending on the observance of DLTs and number of treatment schedules completing the first and second stage. Based on the current practice, we anticipate that the accrual rate will be approximately 3 patients per month, thus requiring up to 20 months for completing the accrual, not counting the mandatory hold times prior to entering the second stage.

Gender of subjects will not be used as a criterion for inclusion or exclusion in this study and there are no restrictions on the accrual of minorities. In the CLL patient population at DFCI, approximately 70% of patients were men and approximately 15% of patients were minorities. Based on this self-reported ethnicity and gender, the anticipated accrual in subgroups defined by gender and race is summarized in the table below. Since the sample size is not fixed, these numbers are based on the maximum sample size of 60. Patients who are enrolled and do not subsequently receive any combination therapy will be replaced in the expansion cohort.

Accrual Targets				
Ethnic Category	Sex/Gender			
	Females		Males	Total
Hispanic or Latino	1	+	2	= 3
Not Hispanic or Latino	17	+	40	= 57
Ethnic Category: Total of all subjects	18	+	42	= 60
Racial Category				
American Indian or Alaskan Native		+	1	= 1
Asian	1	+	2	= 3
Black or African American	1	+	3	= 4
Native Hawaiian or other Pacific Islander		+	1	= 1
White	16	+	35	= 51

Racial Category: Total of all subjects	18	+	42	=	60
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13.3 Randomization: Patients will be randomized in a 1:1:1 ratio using a permuted block algorithm within strata. Randomization will be stratified by age (≥ 65 vs < 65) and deletion 17p status. If one arm is terminated after the first stage, the randomization will be applied to the remaining arms in the expansion phase.

A total of 20 eligible and evaluable patients will be accrued and randomized between the two arms that meet these criteria to gather additional safety and efficacy data. Patients who were enrolled but never received combination therapy may be replaced in the expansion cohort.

13.4 Interim Monitoring Plan. None

13.5 Analysis of Primary Endpoints

Please refer to section 13.1

13.6 Analysis of Secondary Endpoints

As a secondary endpoint, we will evaluate the overall response rate (ORR) if an arm is regarded as safe. In a recent phase III study of ibrutinib in relapsed or refractory CLL, the ORR as a single agent was 63% (including strict IW-CLL response plus PR with lymphocytosis). Basing this as the null hypothesis, we would consider the combination therapy promising if the ORR is 85% or higher. Of 20 patients with a treatment schedule, if 16 or more patients achieve CR or PR as best response, we will regard this treatment schedule efficacious. With this design, the probability of concluding a treatment schedule efficacious is 0.83 if the true but unknown response rate is 85% and 0.09 if the true rate is 63%. This decision rule is calculated using the exact Clopper-Pearson binomial method (Clopper and Pearson, 1934).

Other secondary objectives include assessment of progression-free survival, duration of response, and rate of minimal residual disease. Due to the exploratory nature, the analysis for secondary endpoints will largely be descriptive. Response rate and duration of response will be summarized descriptively and the Kaplan Meier method will be used to estimate the median progression-free survival time and progression-free survival. Association between clinical response and established CLL prognostic factors (ZAP70, FISH cytogenetics, *IGHV* mutation status, *TP53* mutation status) will be tested using Fisher's exact test. A similar descriptive analysis will be performed for laboratory correlative studies of BH3 profiling and genomic markers such as *SF3B1*, *NOTCH1*, and *BCR/NFkB* pathway somatic mutation as well as pharmacodynamic markers. If feasible, association between clinical response and laboratory endpoints will be explored.

13.7 Reporting and Exclusions

Subjects who never start protocol therapy will be excluded from all analyses.

13.7.1 Evaluation of Toxicity

All participants who receive at least one dose of the study treatment will be evaluable for toxicity from the time of their first treatment.

13.7.2 Evaluation of the Primary Efficacy Endpoint

Only those participants who have received at least one cycle of combination therapy and have had their disease re-evaluated will be considered evaluable for response. Each participant will be assigned one of the following categories: 1) complete response, 2) partial response, 3) partial response with lymphocytosis, 4) stable disease, 5) progressive disease, 6) death from toxicity, 7) death because of other cause, or 8) unknown (not assessable, insufficient data). By arbitrary convention, category 8 usually designates the "unknown" status of any type of data in a clinical database.

14. PUBLICATION PLAN

The results should be made public within approximately 2 years of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than approximately 3 years after the end of the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: CLL RESPONSE DEFINITION (HALLEK ET AL. 2008)

Complete Response: (CR)	CR requires all of the following criteria as assessed at least 2 months after completion of therapy: 1. Peripheral blood lymphocytes (evaluated by blood and differential count) below $4 \times 10^9/L$ (4000/μL). 2. Absence of significant lymphadenopathy (e.g., lymph nodes >1.5 cm in diameter) by physical examination. 3. No hepatomegaly or splenomegaly by physical examination and CT. 4. Absence of constitutional symptoms. 5. Blood counts above the following values: • Neutrophils $>1.5 \times 10^9/L$ (1500/μL) without need for exogenous growth factors. • Platelets $>100 \times 10^9/L$ (100 000/μL) without need for exogenous growth factors. • Hemoglobin >110 g/L (11.0 g/dL) without red blood cell transfusion or need for exogenous erythropoietin. For patients in clinical trials, a marrow aspirate and biopsy should be performed at least 2 months after the last treatment and if clinical and laboratory results listed above a-e demonstrate that a CR has been achieved. To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. In some cases, lymphoid nodules can be found, which often reflect residual disease. These nodules should be recorded as "nodular PR." Moreover, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or until peripheral blood counts have recovered. However, this time interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow. In general practice, the use of a marrow biopsy for evaluating a CR is at the discretion of the physician. In clinical trials aiming at maximizing the CR rate, the quality of the CR should be assessed for MRD by flow cytometry or by immunohistochemistry. A controversial issue is how best to categorize the response of patients who fulfill all the criteria for a CR (including the marrow examinations described above) but who have a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity. We recommend that these patients be considered as a different category of remission: CR with incomplete marrow recovery (CRi). For the definition of this category, CRi, the marrow evaluation (described above) should be performed with scrutiny and not show any clonal infiltrate. In clinical trials, CRi patients should be monitored prospectively to determine whether their outcome differs from that of patients with detectable residual or with noncytopenic CR.
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Partial Response: (PR)	<i>To define a PR (partial remission): at least two of the criteria of Group A plus one of the criteria of Group B have to be met. The parameters below should be documented for no less than 2 months. Constitutional symptoms persisting for >1 month should be recorded.</i> <i>Group A</i> - Decrease in the number of blood lymphocytes by 50% or more from the value before therapy. - Reduction in lymphadenopathy (by PE and CT scans) as defined by the following: - A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy. - No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (<2 cm), an increase of less than 25% is not considered to be significant. - Reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more, as detected by CT scan. <i>Group B</i> - Blood count should show one of the following: - Neutrophils $>1.5 \times 10^9/L$ ($1500/\mu L$) without need for exogenous growth factors. - Platelet count $>100 \times 10^9/L$ ($100\,000/\mu L$) or 50% improvement over baseline without need for exogenous growth factors. - Hemoglobin $>110\text{ g/L}$ (11.0 g/dL), or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.
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Chronic Lymphocytic Leukemia Response Definition (Hallek et al. 2008) (continued)

Progressive Disease: (PD)	Progressive disease during or after therapy is characterized by at least one of the following: Lymphadenopathy: Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse. Therefore, the use of imaging methods to follow CLL progression is at the discretion of the treating physician. Disease progression occurs if one of the following events is observed: - Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. - An increase by 50% or more in greatest determined diameter of any previous site. - An increase in the previously noted enlargement of the liver or spleen by 50% or more, or the de novo appearance of hepatomegaly or splenomegaly. - An increase in the number of blood lymphocytes by 50% or more, with at least 5000 B-lymphocytes per μL. - Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy. - Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL <i>During therapy:</i> Cytopenias may occur as a side effect of many therapies. During therapy, cytopenias cannot be used to define disease progression. <i>After treatment:</i> The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by >20 g/L (2 g/dL) or to <100 g/L (10 g/dL), or by a decrease of platelet counts by >50% or to <100 x 10⁹/L (100,000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.
Stable Disease: (SD)	Patients who have not achieved a CR, PR, or nPR and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a non-response).
Nodular Partial Response (nPR)	As per Cheson et al., 2012, patients who achieve a radiographic PR but continue to have a lymphocytosis with >5,000 B-lymphocytes per μL are considered to have a nodular partial response, also known as PR with lymphocytosis, due to the fact that they appear to derive a similar clinical benefit from BCR inhibitors as patients who achieve a traditional PR.

APPENDIX C: IW-CLL GRADING SCALE FOR HEMATOLOGIC TOXICITY IN CLL STUDIES

Grade	Decrease in Platelets [¶] or Hb [‡] (nadir) from Pretreatment Value, %	Absolute neutrophil count/ μ L (nadir) [§]
0	No change to 10%	≥ 2000
1	11% - 24%	≥ 1500 and < 2000
2	25% - 49%	≥ 1000 and < 1500
3	50% - 74%	≥ 500 and < 1000
4	$\geq 75\%$	< 500

Grades: 1, mild; 2, moderate; 3 severe; 4 life-threatening; 5 fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

¶ Platelet decrease, must be below normal levels for grades 1 to 4 at any level of decrease, the platelet count is $< 20 \times 10^9/L$ (20,000/ μ L), this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, $20 \times 10^9/L$ [20 000/ μ L]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

‡ Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§ If the absolute neutrophil count (ANC) reaches $< 1 \times 10^9/L$ (1000/ μ L), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was $< 1 \times 10^9/L$ (1000/ μ L) before therapy, or dependent on growth factors to be $> 1000/uL$, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity, but should be documented.

APPENDIX D: CONTRACEPTIVE GUIDELINES AND PREGNANCY

Women Not of Childbearing Potential are Defined as Follows:

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [for US only: and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Contraceptive Guidelines for Women of Child-Bearing Potential:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for additional 4 weeks after study drug discontinuation. The highly effective contraception is defined as either:

1. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
2. Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomised male partner should be the sole partner for that patient.
4. Use of a combination of any two of the following (a+b):
 - a. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
 - b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

The following are **unacceptable** forms of contraception for women of childbearing potential:

- Oral contraception, injected or implanted hormonal methods are not allowed as ibrutinib potentially decreases the effectiveness of hormonal contraceptives.
- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding

- Fertility awareness
- Withdrawal
- Cervical shield

Women of child-bearing potential must have a negative serum or urine pregnancy test ≤ 72 hours prior to initiating treatment.

Fertile Males:

Fertile males, defined as all males physiologically capable of conceiving offspring must use condom during treatment, for additional 4 weeks after study drug discontinuation, and should not father a child in this period.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Genentech within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to Genentech. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug and reported by the investigator to Genentech. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

APPENDIX E: STUDY PARTICIPANT SELF-ADMINISTERED DRUG DIARY

PATIENT INSTRUCTIONS: Take your medication exactly as prescribed by your doctor. See the next page for specific doses for each medication that you are taking.

Ibrutinib should be kept in its bottle and kept at room temperature.

Ibrutinib:

- Ibrutinib should be taken by mouth once per day. This medication should be swallowed intact with 8 ounces of water (approximately 8 ounces).
- Do not consume grapefruit, grapefruit juice or Seville oranges while taking ibrutinib. Do not take fish oil or vitamin E supplements. Consult your doctor before making any changes to medications or supplements.
- If a dose is missed, it can take it as soon as possible on the same day and you should take dose at the normally scheduled time the next day.
- If you vomit drug, please record this in diary as a missed dose and do not take another dose of drug that day.

FOR CLINIC USE ONLY:
• Give patient all 2 pages of Drug Diary stapled together. Provide one diary per cycle (28 days). • Complete patient identifiers and medical team contact information on page 2. • Complete correct dose levels for ibrutinib on page 2.

APPENDIX E: STUDY PARTICIPANT SELF-ADMINISTERED DIARY

CAPSULE FORMULATION

Participant Identifier: _____ Cycle #: _____

Your MD _____

Phone _____

Your RN _____

Phone _____

STUDY DRUG INSTRUCTIONS:

Take the following medications as indicated below.
Record the dose of each medication on the chart to
the right after taking each day.

Ibrutinib:

☐ 3 x 140 mg capsules by mouth on Days 1-28 (420 mg)

☐ 2 x 140 mg capsules by mouth on Days 1-28 (280 mg)

☐ 1 x 140 mg capsules by mouth on Days 1-28 (140 mg)

Patient Signature: _____ Date: _____

Delegated Study Staff Signature: _____ Date: _____

	Date	Number Taken	Comments
		Ibrutinib	
Ex:	2/1/2015	3	vomited hour later
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			
Day 22			
Day 23			
Day 24			
Day 25			
Day 26			
Day 27			
Day 28			

**APPENDIX E: STUDY PARTICIPANT
SELF-ADMINISTERED DIARY**

TABLET FORMULATION

Participant Identifier: _____ Cycle #: _____

Your MD _____

Phone _____

Your RN _____

Phone _____

STUDY DRUG INSTRUCTIONS:

Take the following medications as indicated below.

Record the dose of each medication on the chart to
the right after taking each day.

Ibrutinib:

☐ 1 x 420 mg capsules by mouth on Days 1-28 (420 mg)

☐ 1 x 280 mg capsules by mouth on Days 1-28 (280 mg)

☐ 1 x 140 mg capsules by mouth on Days 1-28 (140 mg)

Patient Signature: _____ Date: _____

Delegated Study Staff Signature: _____ Date: _____

	Date	Number Taken	Comments
		Ibrutinib	
Ex:	2/1/2015	1	vomited hour later
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			
Day 22			
Day 23			
Day 24			
Day 25			
Day 26			
Day 27			
Day 28			

DFCI IRB Protocol #: 15-283

APPENDIX F

**Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan**

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1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies such as the FDA. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC

Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Matthew Davids, MD will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. Genentech) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.

- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.

- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.
- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening

protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB and will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed or e-mailed to the Coordinating Center. The following must be included in the submission:

- Copy of required laboratory test and required exams/documentation that supports the patient's eligibility
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed eligibility and signed (if used as source documentation) checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms “violation”, “deviation” and “exception” to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution’s IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution’s IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol [section 7](#)

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the [DFCI IRB Adverse Event Reporting Policy](#).

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC CTRIO provides a web based training for all eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol [section 8](#).

Participating Institutions should order their own agent regardless of the supplier. (i.e. pharmaceutical company.)

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

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The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center. These periodic requests may be either virtual, on site, or a combination of both throughout the course of the study. The study monitor will occasionally ask for source documentation to corroborate data that is entered for an upcoming deadline (ie; abstract, manuscript, interim data analysis)

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

At least one study staff member from each participating site is encouraged to participate in monthly Coordinating Center initiated teleconferences.

Remote Monitoring-Participating Institutions will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification according to the trial specific monitoring plan.

and/or

On-Site Monitoring- Source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination depending on the specific circumstances.

The following **minimum** accrual requirements are recommended:

- 1) Phase I: 2 per site/annually

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and

analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor, DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX G GENENTECH SAE REPORTING COVER SHEET

Interventional IIS Supported Study Safety Template



SAFETY REPORTING FAX COVER SHEET Genentech Supported Research

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[] - [] - []
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SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET