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TITLE: A Phase II Study of Ibrutinib in Combination with Fludarabine, Cyclophosphamide, and Rituximab (iFCR) in Previously Untreated, Younger Patients with Chronic Lymphocytic Leukemia

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SYNOPSIS

Study Title: A Phase II Study of Ibrutinib in Combination with Fludarabine, Cyclophosphamide, and Rituximab (iFCR) in Previously Untreated, Younger Patients with Chronic Lymphocytic Leukemia

Study Overview: This is an open-label, phase II study of ibrutinib in combination with fludarabine, cyclophosphamide, rituximab (iFCR) in previously untreated, younger patients with CLL. Patients will start on cycle 1, day -7 with one week of ibrutinib monotherapy at the FDA-approved dose for CLL of 420 mg PO daily, which will allow time for mobilization of CLL cells from lymph nodes and marrow and will also allow for collection of patient samples for correlative studies. FCR will subsequently be introduced on cycle 1, day 1, and administered at standard dosing for up to 6 cycles of approximately 28 days each. Study visits will occur weekly in the first month, biweekly in the second month, and subsequently once per 28-day cycle. Efficacy assessments will be performed at baseline, after cycle 3, and 2 months after completing combination therapy, and will include CT scan, bone marrow biopsy, and minimal residual disease (MRD) analysis on peripheral blood (PB) and bone marrow (BM). At the conclusion of the combination portion (up to 6 cycles), responders will be allowed to continue on ibrutinib maintenance for two years if they do not experience disease progression. During this 2 years of ibrutinib maintenance, patients will be followed with PB MRD testing every 6 months and with a BM MRD assessment at 1 year into maintenance. After 2 years of ibrutinib maintenance, all patients will undergo a repeat bone marrow biopsy. All those who are BM MRD-positive will continue on ibrutinib maintenance and will be monitored with PB MRD assessments every 6 months. . All those who are BM MRD-negative will discontinue ibrutinib and will be followed with PB MRD assessments every 6 months. Those patients who remain PB MRD-negative will remain off ibrutinib. Patients who become PB MRD-positive will have repeat PB MRD testing 3 months later. If PB MRD-negative at that point they will remain off ibrutinib. If confirmed to be PB MRD positive on this second assessment they will resume ibrutinib and continue until progression or unacceptable toxicity.Also, if at any time a patient off ibrutinib has evidence of clinical CLL progression (as assessed by the treating investigator) they will resume ibrutinib at that time.

Primary Objectives

- Part I: To assess the rate of minimal residual disease (MRD) negative complete response (CR) in the bone marrow in younger CLL patients treated upfront with iFCR, as assessed 2 months after completing combination therapy with iFCR
- Part II: To assess the rate of BM MRD-negativity 2 years after ibrutinib discontinuation in patients who achieve BM MRD-negativity after iFCR induction and 2 years of ibrutinib maintenance

Secondary Objectives

- To determine clinical response, including overall response rate, complete and partial response rates, progression free survival, and overall survival by 2008 IW-CLL criteria (Hallek et al., 2008)
- To determine the rate of MRD-negative CR in the bone marrow after 3 cycles of iFCR and at 1 year and 2 years after completing the combination portion of the study

- To determine the rate of conversion of patients in BM MRD-negative PR to BM MRD-negative CR after 1 and 2 years after completing the combination portion of the study
- To determine the time to MRD-negativity for patients who achieve MRD-negativity
- To determine the time to conversion of BM MRD-negativity to MRD-positivity in patients who discontinue ibrutinibTo assess safety and tolerability
- To evaluate the association of established CLL prognostic factors including FISH cytogenetics, *IGHV* mutation status, and *TP53* mutation with clinical response

Exploratory Objectives

- To evaluate the association of novel prognostic factors such as BH3 profiling, *SF3B1, NOTCH1,* and *BCR/NFKB* pathway somatic mutation with clinical response
- To measure pharmacokinetics of ibrutinib as monotherapy in the upfront setting as well as in combination with FCR
- To measure the change in pharmacodynamic markers such as p-AKT, p-BTK, p-ERK, and Ki-67 during initial therapy
- To compare MRD measurements by four-color flow cytometry to those of the Sequenta sequencing technology

Schedule of Administration

Ibrutinib will be administered orally daily during each 28-day cycle. FCR will be given at standard dosing, with dose reductions permitted as per usual standards of care. At the conclusion of a maximum of 6 cycles of iFCR therapy, patients with a partial or complete response regardless of MRD status will be able to continue on to a maintenance phase of ibrutinib monotherapy. After 2 years of ibrutinib maintenance, if they are BM MRD negative, patients will discontinue ibrutinib, whereas if they are BM MRD positive they will continue ibrutinib monotherapy maintenance until the time of progression or unacceptable toxicity Patients who discontinue ibrutinib who later convert to PB MRD-positivity on two consecutive readings will resume ibrutinib monotherapy maintenance.

Definition of Unexpected Toxicities

Unexpected toxicities would include the following events that occur during the first cycle of iFCR treatment, unless they are clearly due to extraneous causes: grade 4 or higher infusion reaction, grade 4 or higher infection, or other grade 3 or higher, clinically significant non-hematologic toxicity related to study treatment, except asymptomatic laboratory abnormalities or nausea/vomiting/diarrhea that improves with supportive care.

Grade 3 or 4 drug-related toxicities occurring after the first cycle of treatment will be discussed with the Principal Investigator and will be considered in decisions regarding the recommended dose for future studies.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 will be used to grade toxicities during the trial unless otherwise specified (Appendix D).

Study Drug

Ibrutinib is administered orally as a capsule formulation. The ibrutinib drug product is supplied as 140 mg formulated capsules.

Inclusion Criteria

Laboratory

- Adequate hematologic function independent of growth factor support for at least 7 days prior to screening and randomization, with the exception of pegylated G-CSF (pegfilgrastim) and darbopoeitin which cannot be administered within 14 days of screening. Patients must meet the following hematologic criteria:
  - Absolute neutrophil count ≥750 cells/mm^3 (0.75 x 10^9/L)
  - Platelet count ≥50,000 cells/mm^3 (50 x 10^9/L)
  - Hemoglobin ≥ 8 g/L

- Adequate hepatic and renal function defined as:
  - Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x institutional upper limit of normal (ULN)
  - Bilirubin ≤1.5 x institutional ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
- Inadequate renal function defined by serum creatinine >1.5 x institutional ULN
- PT/INR <1.5 x institutional ULN and PTT (aPTT) <1.5 x institutional ULN.

Demographic

- Must have a confirmed diagnosis of CLL or SLL as per IW-CLL 2008 criteria
- Must require therapy by standard IWCLL 2008 criteria
- No prior CLL-directed therapy that was instituted due to patient previously meeting IWCLL 2008 criteria for treatment
- Age greater than or equal to 18 years and less than or equal to 65
- ECOG performance status ≤1 (see Appendix A)
- 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
- Ability to understand and the willingness to sign a written informed consent document

Exclusion Criteria

Concurrent Conditions

- 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.
- 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 within 4 weeks of first dose of study drug.
- Recent infection requiring systemic treatment that was completed ≤14 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 with 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*.
- 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.
- 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)
- 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 (other anticoagulants are allowed after consultation with the Principal Investigator).
- Subjects who received a strong cytochrome P450 (CYP) 3A inhibitors within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor(see Appendix B).
- 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 Principal Investigator would place the patient at undue risk or interfere with the study
- Unable to receive prophylactic treatment for pneumocystis
- Patients with del(17p) confirmed by FISH in ≥20% of cells or on stimulated karyotype
- Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix C)

Statistical Methodology

Primary Endpoints:

- Part I: Rate of MRD-negative complete response (CR) in the bone marrow assessed at 2 months after completing the combination therapy.
- Part II: Rate of BM MRD-negativity 2 years after ibrutinib discontinuation in patients who achieve BM MRD-negativity after iFCR induction and 2 years of ibrutinib maintenance

Study Design/Sample Size

Part I was a one-stage, single-arm, phase 2 study to determine the MRD-negative CR rate in the bone marrow after treating with iFCR in previously untreated, younger CLL patients. In the previous study with FCR alone without ibrutinib in a similar patient population, the MRD-negative CR rate was 20% (Boettcher et al., 2012). We base this as the null hypothesis. With the addition of ibrutinib, we hypothesize that the MRD-negative CR rate will be 40% or higher. Thirty-five patients will be enrolled and if 11 or more patients achieve MRD-negative CR at 2 months post iFCR treatment, we will regard the treatment efficacious. Conversely, if 10 or fewer patients achieve MRD-negative CR, we will regard the treatment inefficacious. With this design, the probability of concluding the treatment efficacious is 0.89 if the true but unknown response rate is 40% and 0.075 if the true rate is 20%. This decision rule is calculated using the Clopper-Pearson exact binomial method**.**

Part II is an expansion cohort in which we will investigate whether discontinuation of ibrutinib for those patients who achieve bone-marrow (BM) MRD-negativity and receive 2-years of ibrutinib maintenance therapy is feasible without compromising efficacy. For this objective, we will continue to enroll 50 additional patients to the current study to a total of 85 patients. Of these 85, we anticipate that approximately 60 patients (20 from the current cohort of 35 and 40 from the additional 50 patients) will be eligible for Part II. Although the MRD-negative rate is estimated to be 86% in the current cohort of 35 patients, they are allowed to continue treatment and we project that approximately two-thirds of them will decide to discontinue upon completion of the maintenance therapy. Therefore, approximately 20 patients from the current cohort would be eligible for Part II.

Accrual Rate

To accrue 38 patients with MRD-CR, we will accrue a total of 85 patients in this study. Patients who are inevaluable for response may be replaced. Since 35 have already been accrued, an additional 50 patients will be accrued to this new portion of the study. Based on the accrual of Part I of this study and knowing that we no longer have a competing study and are adding 2 new external sites, we anticipate accrual at a rate of about 2.75 patients per month such that the accrual of this study will complete within approximately 18 months from the start of randomization.

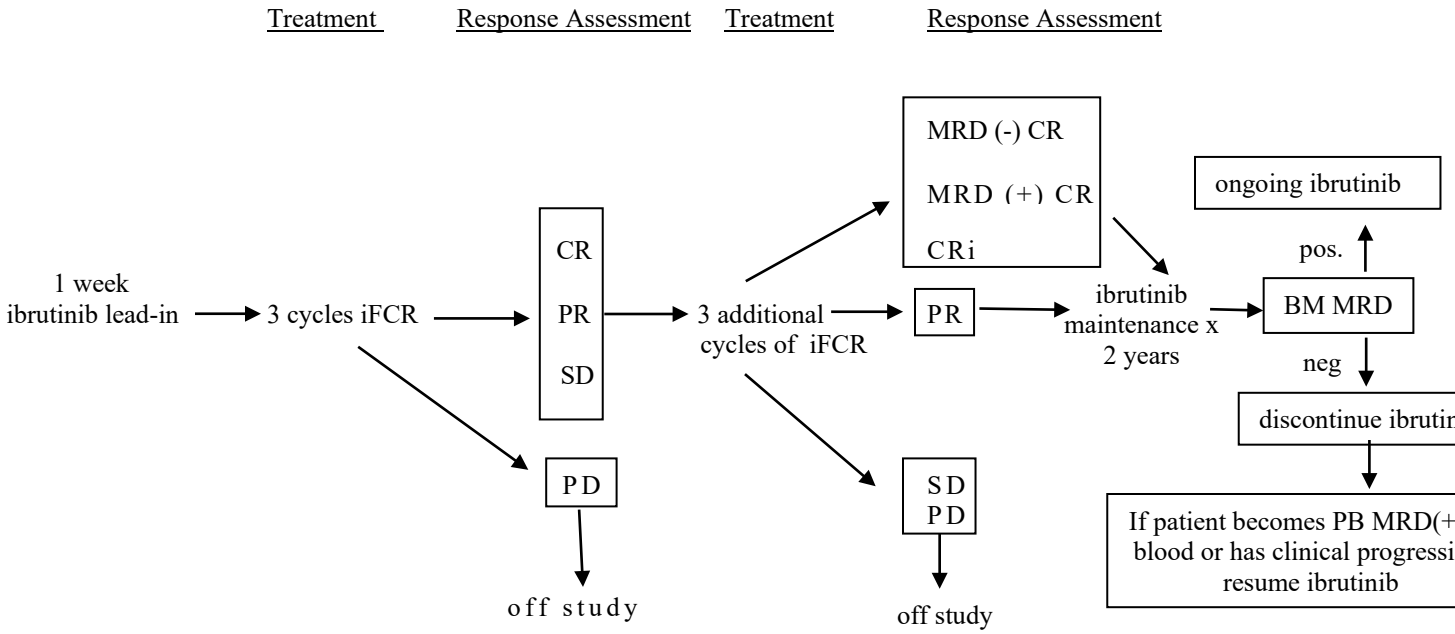
Monitoring Treatment Related Toxicity

If in the first 10 patients who receive at least one cycle of iFCR, 3 or more patients develop unexpected toxicity (see above), this will trigger a consultation with the DSMC about whether to stop accrual. With this design, the probability of triggering a consultation is 0.07 if the true but unknown rate of grade 3 or higher treatment related toxicity is 10%, 0.18 if the rate is 15%, 0.74 if the rate is 35%, and 0.83 if the rate is 40%.

Analysis of Secondary Endpoints

The analysis of secondary endpoints will be primarily descriptive, including proportions of the rate of MRD-negative CR in the bone marrow after 3 cycles of iFCR and at 1 year and 2 years after completing the combination portion of the study. Time to MRD-negativity will also be analyzed for patients who achieve MRD-negativity. Associations between the clinical outcome and baseline factors will be tested using Fisher's exact test, chi-square test and Wilcoxon-rank-sum test. The Kaplan Meier (KM) method will be used to summarize progression-free survival and overall survival descriptively. Association between MRD-negative CR and progression-free and overall survival will be tested using Mantel-Byar test (Mantel et al., 1974). Also, if the number of events permits, we will attempt to construct a multivariable proportional hazards model treating MRD-negative CR status as a time dependent variable. Similar univariable and multivariable (if the number of events permits) analysis will be performed for the best MRD negative response and the kinetics of MRD disappearance over time. Association of established CLL prognostic factors (e.g. FISH cytogenetics, *IGHV* status, ZAP70 status) and clinical response, in particular, MRD-negative CR, will be assessed using primarily univariable logistic regression analysis. In addition, appropriate data analysis will be performed for each of laboratory correlative studies.

SCHEMA



Definitions

MRD (-) CR – Minimal Residual Disease Negative Complete Response
MRD (+) CR – Minimal Residual Disease Positive Complete Response
CRi – Complete Response with incomplete count recovery

PR - Partial Response
PD - Progressive Disease
SD - Stable Disease

PB – Peripheral Blood
BM – Bone Marrow

FCR – Fludarabine, Cyclophosphamide, Rituximab
i – ibrutinib

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1. OBJECTIVES

1.1 Study Design

This is an open-label, phase II study of ibrutinib in combination with fludarabine, cyclophosphamide, rituximab (iFCR) in previously untreated, younger patients with CLL. Ibrutinib will be given at 420 mg PO daily, the dose that is FDA-approved in CLL subjects. Patients will start on cycle 1, day -7 with one week of ibrutinib monotherapy, which will allow time for mobilization of CLL cells from lymph nodes and marrow and will also allow for collection of patient samples for correlative studies. After the 7 day ibrutinib lead-in period, FCR will subsequently be introduced on cycle 1, day 1, and administered at standard dosing for up to 6 cycles. Study visits will occur weekly in the first month, biweekly in the second and subsequently once per 28-day cycle. Disease assessments will be performed at baseline, after cycle 3, and 2 months after completing combination therapy, and will include CT scan, bone marrow biopsy, and minimal residual disease (MRD) analysis on peripheral blood and bone marrow. The primary endpoint is the rate of bone marrow MRD-negativity in patients achieving CR by IW-CLL criteria 2 months after completing combination iFCR. At the conclusion of the combination portion, responders will be allowed to continue on ibrutinib maintenance for 2 years. During this 2 years of ibrutinib maintenance, patients will be followed with PB MRD testing every 6 months and with a BM MRD assessment at 1 year into maintenance. After 2 years of ibrutinib maintenance, all patients will undergo a repeat bone marrow biopsy. All those who are BM MRD-positive will continue on ibrutinib maintenance and will be monitored with PB MRD assessments every 6 months. All those who are BM MRD-negative will discontinue ibrutinib and will be followed with PB MRD assessments every 6 months. Those patients who remain PB MRD-negative will remain off ibrutinib. Patients who become PB MRD-positive will have repeat PB MRD testing 3 months later. If PB MRD-negative at that point they will remain off ibrutinib. If confirmed to be PB MRD positive on this second assessment they will resume ibrutinib and continue until progression or unacceptable toxicity. Also, if at any time a patient off ibrutinib has evidence of clinical CLL progression (as assessed by the treating investigator) they will resume ibrutinib at that time.

1.2 Primary Objectives

- Part I: To assess the rate of minimal residual disease (MRD) negative complete response (CR) in the bone marrow in younger CLL patients treated upfront with iFCR assessed 2 months after completing the combination portion of the studyPart II: To assess the rate of BM MRD-negativity 2 years after ibrutinib discontinuation in patients who achieve BM MRD-negativity after iFCR induction and 2 years of ibrutinib maintenance

1.3 Secondary Objectives

- To determine clinical response, including overall response rate, complete and partial response rates, progression free survival, and overall survival by 2008 IW-CLL criteria (Hallek et al., 2008)

- To determine the rate of MRD-negative CR in the bone marrow after 3 cycles of iFCR and at 1 year and 2 years after completing the combination portion of the study
- To determine the rate of conversion of patients in BM MRD-negative PR to BM MRD-negative CR after 1 and 2 years after completing the combination portion of the study
- To determine the time to MRD-negativity for patients who achieve MRD-negativity
- To determine the time to conversion of BM MRD-negativity to MRD-positivity in patients who discontinue ibrutinib
- To assess safety and tolerability
- To evaluate the association of established CLL prognostic factors including FISH cytogenetics, *IGHV* mutation status, and *TP53* mutation status with clinical response

1.4 Exploratory Objectives

- To evaluate the association of novel prognostic factors such as BH3 profiling, *SF3B1, NOTCH1,* and *BCR/NFKB* pathway somatic mutation with clinical response
- To measure pharmacokinetics of ibrutinib as monotherapy in the upfront setting as well as in combination with FCR
- To measure the change in pharmacodynamic markers such as p-AKT, p-BTK, p-ERK, and Ki-67 during initial therapy
- To compare MRD measurements made by four-color flow cytometry to those made with the Sequenta sequencing technology

2. BACKGROUND

2.1 Study Disease

Background
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 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 for 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). In that trial, FCR produced an OR rate of 90% with CR rate of 44% and a median PFS of nearly 5 years. Moreover, several patients with favorable prognostic markers remain disease free now more than 10 years out after completing therapy, raising the possibility of cure in a small subset of patients.

Limitations of Current Therapy
Because of these encouraging results, FCR has become the standard of care for previously untreated, younger patients. Despite the impressive overall response rates with FCR, only 20% of patients achieve minimal residual disease (MRD) negativity in the bone marrow at their final restaging (Boettcher et al., 2012), and it is unlikely that patients can achieve cure without first achieving MRD-negativity. Indeed, patients who achieved low MRD levels after three treatment cycles had the same PFS as those who completed six cycles, suggesting that attainment of MRD-negativity is the best predictor of long PFS.

Though clearly a powerful regimen, FCR on its own has some significant limitations in terms of efficacy. For example, patients with high risk markers such as del(17p) have markedly inferior outcomes, with a poor CR rate (5%) and 3-year progression-free (18%) and overall survival (38%). Furthermore, patients in all risk groups receiving FCR inevitably relapse. Younger patients with CLL typically exhaust conventional treatment options after a few years, and therefore improved treatment options for this patient population in particular are urgently needed.

B Cell Receptor Pathway
B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development (Shaffer 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

Over the last few years, it has been recognized that the B cell receptor (BCR) pathway is a promising, novel 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. Upregulation of the B cell receptor (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).

Ibrutinib monotherapy
Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. In early phase clinical trials in relapsed/refractory B cell malignancies, the drug has been extremely well-tolerated, with most of the adverse events being grade 1 or 2 in severity and self-limited. Durable responses to ibrutinib 420 mg daily have been observed in the majority of patients with relapsed refractory CLL (Byrd et al., 2013). Ibrutinib (IMBRUVICA ™) is approved by the U.S. Food and Drug Administration (FDA)and the EU for the treatment of patients with chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) who have received at least one prior therapy. Ibrutinib is currently under investigation in various indications. Although ibrutinib does not yet carry a label for previously untreated CLL, including CLL with a deletion of the short arm of chromosome 17 (del17p) or a TP53 mutation, and patients with Waldenstrom's macroglobulinemia. Ibrutinib is currrently under investigation in various indications as a single agent and in combinations. Ibrutinib monotherapy has been shown to be safe and effective in the frontline setting, with a 71% objective response rate, including a 13% complete response rate, and after a median follow-up of

22.1 months, the median PFS has not been reached (O'Brien et al., 2013). Ibrutinib has also been safely given in combination with chemoimmunotherapy, as detailed in Section 2.2.2.

2.2 Study Agents

2.2.1 Fludarabine, Cyclophosphamide, Rituximab (FCR)

Fludarabine is an FDA-approved intravenous chemotherapy agent that forms the backbone of the FCR regimen. Its mechanism of action is as a purine analogue, and it is dephosphorylated in plasma to its active metabolite, which is primarily excreted in the urine. Its safety profile is well-characterized and available on the package label. Fludarabine will be dosed as per the standard of care dosing in the FCR regimen (Hallek et al., 2010).

Cyclophosphamide is an FDA approved intravenous chemotherapy agent that when combined with fludarabine was found to have significantly higher efficacy than fludarabine alone (O'Brien et al., 2001). Its mechanism of action is mainly as an alkylating agent, and it is hepatically metabolized to active metabolites that are primarily excreted renally. Its safety profile is well-characterized and available on the package label. Cyclophosphamide will be dosed as per the standard of care dosing in the FCR regimen.

Rituximab is an FDA-approved chimeric anti-CD20 monoclonal antibody originally developed and approved for the treatment of low-grade non-Hodgkin's lymphomas, in which it has high response rates as a single agent in the upfront and relapsed settings. Initial experience with single-agent rituximab at the standard approved dose of 375 mg/m2 weekly for 4 weeks in relapsed CLL was disappointing, with reported response rates between 7 and 35%; however, improved results in CLL have been seen with dose-intensification in both the relapsed setting and in upfront therapy, and in combination either with fludarabine, or fludarabine and cyclophosphamide (Byrd et al., 2005, Hallek et al., 2010). Rituximab is cleared by the reticuloendothelial system. Its safety profile is well-characterized and available on the package label. Rituximab will be dosed as per the standard of care dosing in the FCR regimen.

2.2.2 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, LLC,as IMBRUVICA ™, and is approved by the U.S. Food and Drug Administration (FDA) and the EU for the treatment of patients with CLL including CLL with a 17p deletion, and TP53 mutation and mantle cell lymphoma who have received at least one prior therapy. Ibrutinib is also approved for treatment for Waldenstrom's macroglobulinemia. 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.

2.3 Nonclinical Studies

2.3.1 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 (IC50 = 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 (IC50 = 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).

2.3.2 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).

2.3.3 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.

2.4 Clinical Studies

2.4.1 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 (t1/2) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (Tmax) 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 Tmax delayed from 2 to 4 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The On-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady state exposure of ibrutinib and and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) 30 ml/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administation, the AUC of ibrutinib increased 2.1-,8.2-, and 9.8- fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C[see Appendix C]) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adversse reactions were reported in patients with B-cell malignancies (CLL, MCL, and WM) with mild hepatic impairment based on NCI organ dysfunctions working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function..

2.4.2 Clinical Efficacy Studies in Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Subjects with CLL or SLL have received single-agent PCI-32765 across 2 published clinical studies: 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 signals in this study were in CLL/SLL (11 of 16 patients responded (two CRs)), MCL (7 of 9 patients responded (three CRs)), and WM (3 of 4 patients responded, no CRs observed) (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

Eighty-five patients with relapsed 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%.

Previously untreated

Thirty-one patients with previously untreated CLL/SLL were also enrolled on this study, and the results were recently reported (O'Brien et al., 2013). To qualify, patients had to be aged at least 65 years and have symptomatic CLL or SLL requiring therapy by IW-CLL criteria. The median age was 71 years (range 65-84), and the incidence of high risk cytogenetic abnormalities was low (only 2 patients with del(17p) and 1 patient with del(11q)). About half of the patients had unmutated IGHV. Twenty-two of 31 patients (71%) achieved an objective response, including 4 patients (13%) with a CR and 1 patient (3%) with a nodular PR. An additional four (13%) patients achieved a partial response with lymphocytosis. The median follow-up on this study remains short for a front line study at 22.1 months, and at this early time point the median PFS has not yet been reached, with only 1 patient having progressed during follow-up. These promising initial results were recently confirmed in a large, randomized phase III study of ibrutinib vs. chlorambucil in frontline therapy for CLL patients (Burger et al., N Engl J Med, 2015), leading to a full FDA approval for ibrutinib for frontline CLL therapy.

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., 2013). 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 (Jaglowski 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.

Ibrutinib plus Chemoimmunotherapy

Though older patients and those with co-morbidities often experience significant toxicity with chemoimmunotherapy (CIT), younger patients may derive benefit from the deep responses achieved by these regimens, in particular FCR. For example, about 20% of patients achieved an MRD-negative CR in the bone marrow with front line FCR, and several of these patients went on to have durable remissions lasting 10 years or more (Boettcher et al., 2012). Therefore, a logical avenue to explore is the combination of ibrutinib with CIT to try to enhance these responses further.

The final results of a phase 1b study of ibrutinib in combination with bendamustine plus rituximab (BR) for relapsed/refractory CLL were recently reported (Brown et al., 2013). Thirty patients with CLL/SLL with a median age of 62 years and a median of 2 prior therapies were treated with ibrutinib with continuous dosing at 420 mg daily along with up to 6 cycles of BR, followed by ibrutinib maintenance. The combination was well-tolerated, and the overall response rate was 93%, including 5 CRs, 3 nodular PRs, and 20 PRs, with one additional patient achieving PR with lymphocytosis. The estimated 15 month PFS was 78%, and responses were independent of high-risk features. These results provided a strong rationale for the development of a phase 3 study of BR plus or minus ibrutinib, which is now ongoing.

Preliminary Data for Ibrutinib plus FCR

As part of this same phase 1b study, we treated 3 younger patients with a median age of 56 years with ibrutinib in combination with FCR at standard dosing. All 3 patients completed 6 cycles of therapy and 2 of these patients achieved CR, while a nodular PR was observed for the remaining patient. The patient with a nodular PR continued on ibrutinib and subsequently improved his response to MRD positive CR. The dramatic responses and excellent tolerability we observed in these three patients inspired us to pursue the ibrutinib plus FCR combination in a larger study.

Results of Part I of the Current Phase II Study of Ibrutinib + FCR (iFCR)

We presented the preliminary results of part I of this study at the 2016 American Society of Hematology Annual Meeting (Davids et al., 2016 ASH Meeting, Abstract 3243).

As of August 1, 2016, the study reached full accrual at 35 pts. The median age at enrollment was 55 yrs (range 38-65). 9/33 tested (27%) had del(11q) and 4/33 tested (12%) had del(17p). Unmutated *IGHV* was present in 20/31 tested (65%), ZAP-70 was positive in 21/32 tested (66%), *TP53* mutation was present in 2/31 tested (6%), and *NOTCH1* mutation was present in 2/21 tested (10%).

We initially enrolled 10 pts in a safety lead-in cohort and did not see any unexpected toxicities. In the entire cohort of 35 pts, hematologic toxicity included grade (gr) 4 neutropenia in 1 pt (3%), as well as gr 3 neutropenia (15%), thrombocytopenia (18%), and anemia (6%). All grade non-hematologic toxicities occurring in >15% of pts included nausea (68%), bruising (35%), fatigue (29%), and rash (21%) (all gr 1/2) and diarrhea (21%) (all gr 1). The only bleeding events were gr 1 epistaxis in 2 pts. SAEs included gr 4 febrile neutropenia, gr 3 atrial fibrillation, gr 3 transaminitis, gr 3 pneumonia, and gr 3 appendicitis in 1 pt each. 9% of pts experienced ≥gr 3 infection. A median of 6 cycles of FCR were given (range 3-6). One pt had

ibrutinib dose reduction (pt with febrile neutropenia), and 18% of pts had at least 1 dose reduction of chemotherapy.

Twenty-eight pts have undergone primary endpoint re-staging after completing the iFCR combination and 26 pts have been tested for BM MRD. In these 26 pts, the rate of CR with BM MRD-neg is 39% (10/26). In the 28 pts with re-staging, the ORR is 100%, including 39% (11/28) with CR or CRi. 17/28 (61%) pts had a PR, and all 17 PR pts have residual lymph nodes ≤ 2.5 cm in long axis by CT imaging. BM was MRD-neg in 23/26 tested (89%), including 13/17 (76%) of pts in PR. With a median follow-up of 12.1 months (range 0.1-21.1), all pts are alive, and 33 of the 35 pts remain on treatment. One pt who completed 6 cycles of iFCR and achieved CR with BM MRD-neg declined ibrutinib maintenance and remains in MRD-neg CR at 10 months off therapy, and one pt with del(17p) achieved MRD-pos PR and elected to pursue allogeneic stem cell transplant.

Overall, iFCR induced deep responses in previously untreated young CLL pts, with 39% of evaluable pts achieving CR with BM-MRD-neg and 89% achieving BM MRD-neg, significantly higher than the 20% rate seen historically with FCR alone. Low rates of hematologic and infectious toxicities were observed, possibly due to mandatory use of growth factor support and antimicrobial prophylaxis. 76% of PR pts have achieved BM MRD-neg, and all of these pts have small residual lymph nodes.

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 untreated 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.

2.4.3 Overall Safety Summary

A brief summary of safety data from monotherapy and combination therapy studies is provided in below. For more comprehensive safety information please refer to the current version of the IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, USPI, SmPC).

For monotherapy studies:

Pooled safety data for a total of 1318 subjects treated with ibrutinib monotherapy from 13 studies that have completed primary analysis or final analysis as of the 31 May 2016 cutoff date for the current IB update in B-cell malignancies are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1318):

Most frequently reported TEAEs >15% [a]	Most frequently reported Grade 3 or 4 TEAEs >3% [b]	Most frequently reported Serious TEAEs >2% [c]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Pyrexia	Hypertension	
Anemia	Diarrhea	
Neutropenia	Atrial fibrillation	
Upper respiratory tract infection		
Thrombocytopenia		
Oedema peripheral		

[a] Source is Table 6 of IB (v10), [b] Source is Table 8 of IB (v10), [c] Source is Table 9 of IB (v10).

For more detailed information refer to the current version of the IB.

For combination therapy studies:

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies, which included 1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs >20% [a]	Most frequently reported Grade 3 or 4 TEAEs >3% [b]	Most frequently reported Serious TEAEs >2% [c]
Neutropenia	Neutropenia	Pneumonia
Diarrhea	Thrombocytopenia	Febrile neutropenia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anemia	Anemia	
Pyrexia	Fatigue	
	Hypertension	
	Diarrhea	

a Source is Table 10 of IB (v10), b Source is Table 12 of IB (v10), c Source is Table 13 of IB (v10).

For more detailed information refer to the current version of the IB.

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).

2.4.4 Hemorrhagic Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 5.3.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4.1 for guidance on ibrutinib management with surgeries or procedures. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed, refer to Section 5.3.4.

2.4.5 Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have

an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 6.4.1).

2.4.6 Rash

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

2.4.7 Non-Melanoma Skin Cancer

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

2.4.8 Infection

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (reference Section 5.3). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

2.4.9 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Subjects should be monitored for fever, weakness, or easy bruising and/or bleeding.

2.4.10 Lymphocytosis and Leukostasis

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/µL) may confer increased risk. For subject and ibrutinib management guidance, refer to section 6.2.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/ small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy and typically resolves within a median of 8.0 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL. This pharmacodynamic effect was less prominent or not observed in other indications.

A large increase in the number of circulating lymphocytes (eg, >400,000/μL) has been observed in some subjects. Lymphocytosis was not commonly observed in subjects with Waldenström's macroglobulinemia treated with ibrutinib. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

2.4.11 Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

2.4.12 Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines.

2.4.13 Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines.

2.4.14 Hypertension

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

2.4.15 Drug-Drug Interaction

Ibrutinib is primarily metabolized by cytochrome CYP3A. During the initial week of ibrutinib monotherapy, the concomitant use of strong CYP3A inhibitors or inducers is prohibited due to their potential confounding effects on pharmacokinetics and pharmacodynamics correlative studies. After the initial week, 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 CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, reduce ibrutinib dose to 140 mg for the duration of the inhibitor use or withhold ibrutinib treatment temporarily (for 7 days or less). Subjects should be monitored for signs of ibrutinib toxicity.

- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg (for 840 mg/day dose, reduce to 280 mg) for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Appendix B).

- No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix B. A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

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.

2.5 Rationale

Although FCR is highly active against CLL cells in the blood, our group and others have shown that CLL cells in stromal sanctuary sites such as the bone marrow and lymph nodes benefit from pro-survival signals from the microenvironment, and are therefore less likely to undergo apoptosis in response to chemotherapy. We showed that stroma can decrease the propensity of CLL cells to undergo apoptosis, and that BCR inhibition is able to restore this propensity and thereby restore sensitivity of CLL cells to other therapies (Davids et al., 2012). Thus, CLL cells protected by stroma may represent a key reservoir of resistant disease that later leads to relapse, even in patients who initially respond well to therapy.
For older, less fit patients, utilizing a non-chemotherapy based strategy such as ibrutinib monotherapy or rational combinations of targeted inhibitors has the potential to provide several years of response with more tolerable toxicity than chemotherapy; however, most of these patients will have persistent disease and will inevitably progress. For younger patients with a long life expectancy, achieving only a few years of remission is inadequate.
The high level of activity of single-agent ibrutinib, its mechanism of action (which is distinct from cytotoxic therapy), and its ability to mobilize CLL cells from protective niches all suggest that combining it with the most effective standard therapy, FCR, might potentially lead to cure. In our pilot data of 3 younger patients who received iFCR, all 3 patients achieved deep remissions, including 2 MRD-negative CR's, without any unexpected toxicities. Since younger patients such as these typically tolerate combination chemotherapy well and desire to maximize long-term remission, they may benefit from an intensive therapeutic approach designed to optimize curative potential, similar to the treatment paradigm used for curable aggressive lymphomas like diffuse large B cell lymphoma.

Unlike older patients who may benefit from a non-chemotherapy approach, for younger patients, it may be appropriate to accept some toxicity with the iFCR combination, with the goal of achieving a more durable response, potentially even a cure. The side effect profiles of ibrutinib and FCR are generally non-overlapping, but given that this combination has only previously been piloted in 3 other patients, our study will closely scrutinize safety for all patients, and in particular for the first 10 patients who complete at least 1 cycle of combination therapy. If unexpected toxicity is observed in 3 or more of these patients, this will trigger a review by the Data Safety Monitoring Committee to determine whether additional patients should be accrued.
The primary objective of our study is to improve the rate of MRD-negative CR in the bone marrow in this patient population. Achieving and sustaining MRD negative CR is the first step toward possible cure. In practice, many studies have established that achievement of MRD

negativity correlate with longer progression-free survival to a variety of different regimens. For example, in the phase III CLL8 FCR study, patients who achieved MRD-negativity after 3 cycles of therapy had a similar PFS as patients who achieved MRD-negativity after the full 6 cycles, suggesting that achieving MRD-negativity is the key to having a durable response (Boettcher et al., 2012). We will be measuring MRD-negativity by four-color flow cytometry with a detection level of 10-4, which has been validated as highly accurate in comparison to PCR-based assays (Rawstron et al., 2013). By utilizing a surrogate endpoint of MRD-negativity as our primary endpoint, we will be able to obtain a rapid assessment of efficacy without having to wait several years for PFS and OS data to mature. This will allow us to efficiently determine whether the iFCR regimen is worthy of exploration in a larger, randomized clinical trial to more definitively assess its efficacy.

2.5.1 Rationale for Ibrutinib Discontinuation

Recent datasets have been published which describe the long term outcomes of patients treated with FCR alone as initial therapy for CLL suggesting that a subset of patients can enjoy long term disease free survival without the need for additional therapies. For example, patients with mutated IGHV CLL treated at MD-ACC on the FCR300 study had a plateau in the PFS curve, with no relapses beyond 10.4 years in 42 patients (Thompson et al., 2016). A similar study from the German CLL Study Group found that the median PFS for patients with mutated *IGHV CLL* was not reached at a median follow-up of 5.9 years (Fischer et al., 2016). Based on the emergence of these data, it is likely that a significant number of CLL patients who receive ibrutinib + FCR plus 2 years of ibrutinib maintenance will be cured of their CLL. The initial design of this study committed all patients to lifelong ibrutinib therapy, but in light of the newly published data, we will now allow patients who achieve MRD-negativity after iFCR plus 2 years of ibrutinib maintenance to discontinue ibrutinib, which will provide important data as to whether indefinite ibrutinib therapy is necessary for such patients. Those patients who develop MRD-positivity after discontinuation will resume ibrutinib therapy and therefore the risks for such patients are minimal.

2.6 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 the iFCR clinical 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 iFCR.

Pharmacodynamic Markers
Where possible, pharmacodynamic markers may be assessed to determine how effectively ibrutinib is hitting its proposed target in vivo in these previously untreated CLL patients. Using pretreatment and week 1 patient samples, we will use phosphoflow cytometry to determine the levels of phospho-AKT, phospho-ERK, and phospho-BTK compared to total AKT, ERK, and BTK, respectively. These analyses may be confirmed in a subset of patients by Western Blot. In addition, recent work has suggested that reduction in the cell proliferation marker Ki-67 in peripheral blood CLL cells occurs rapidly in patients treated with BCR pathway antagonists, and we may assess this also by phosphoflow cytometry.

Sequenta 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. Sequenta, 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 can then be 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.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

Unless otherwise specified, laboratory tests required for eligibility must be completed within 2 weeks prior to study registration. Baseline tumor measurements by CT scan must be performed within 4 weeks of starting study treatment, and bone marrow biopsy must be performed within 3 months prior to study treatment.

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 lymphocyticlymphoma. 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 No 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 and less than or equal to 65. Because CLL is extremely rare in persons <18 years of age, children are excluded from this study. Because iFCR is an aggressive therapy that is likely to be less well-tolerated even in fit elderly subjects, persons > 65 years of age are excluded

3.1.4 ECOG performance status <1 (see Appendix A)

3.1.5 Adequate hematologic function independent of growth factor support for at least 7 days prior to screening and randomization, with the exception of pegylated G-CSF (pegfilgrastim) and darbopoeitin which cannot be administered within 14 days of screening.

Patients must meet the following hematologic criteria at screening:

- Absolute neutrophil count ≥750 cells/mm3 (0.75 x 109/L).
- Platelet count ≥50,000 cells/mm3 (50 x 109/L).
- Hemoglobin ≥ 8 g/L

3.1.6 Adequate hepatic and renal function defined as:

- Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x institutional upper limit of normal (ULN)

3.1.7 Bilirubin ≤1.5 x institutional ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)

3.1.8 Adequate renal function defined by serum creatinine <1.5 x institutional ULN

3.1.9 PT/INR <1.5 x institutional ULN and PTT (aPTT) <1.5 x institutional ULN

3.1.10 The effects of ibrutinib on the developing human fetus are unknown. For this reason and because similar agents are known to be teratogenic, 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. A tubal ligation is sufficient documentation that a patient is not of child bearing potential.

3.1.11 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 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.

3.2.2 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.

3.2.3 Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.

3.2.4 Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.

3.2.5 Recent infection requiring systemic treatment that was completed

3.2.6 Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.

3.2.7 History of stroke or intracranial hemorrhage within 6 months prior to enrollment.

3.2.8 Known history of human immunodeficiency virus (HIV) or active with 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.

3.2.9 Any uncontrolled active systemic infection.

3.2.10 Major surgery within 4 weeks of first dose of study drug.

3.2.11 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.

3.2.12 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.

3.2.13 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.

3.2.14 Lactating or pregnant

3.2.15 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).

3.2.16 Patients receiving any other study agents.

3.2.17 Patients with known CNS involvement

3.2.18 Baseline QTcF >480 ms. NOTE: This criterion does not apply to patients with a left bundle branch block.

3.2.19 Patients who require warfarin or other vitamin K antagonists for anticoagulation (other anticoagulants are allowed after consultation with the Principal Investigator).

3.2.20 Subjects who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor (see Appendix B).

3.2.21 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

3.2.22 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

3.2.23 Unable to receive prophylactic treatment for pneumocystis

3.2.24 Patients with del(17p) confirmed by FISH in ≥20% of cells or on stimulated karyotype

3.2.25 Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix C)

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

3.3.1 Inclusion of women, minorities and other underrepresented populations is encouraged.

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)ODQ central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment 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 ODQODQ protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. 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 may 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 Time. In emergency situations when a participant must begin treatment 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:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. 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 the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the ODQ at 617-632-2295.

4. The ODQ Registrar will (a) review the eligibility checklist, and (b) register the participant on the protocol.

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

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at DFCI by the Research Project Manager. All sites should call the Research Project Manager to verify treatment availability.

Following registration, participants should begin protocol treatment within 3 business days or as soon as possible. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status may be canceled. The Study Coordinator should be notified of participant status changes as soon as possible.

4.4 Registration Process for Other Participating Institutions

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 to the Research Project Manager at the lead site:

- Documentation of diagnosis, prior therapy, baseline assessments and any other documentation relevant to the inclusion/exclusion criteria (see section 3 for details)
- Signed participant consent form
- HIPAA authorization form (if appropriate)
- DF/HCC Eligibility checklist (provided by DFCI Research Manager)

The research nurse or data manager at the participating site will then call 617-632-3539 or e-mail the Research project Manager 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 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 with the ODQ can only be conducted during the business hours of 8am – 5pm ET Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for fludarabine, cyclophosphamide, rituximab, and ibrutinib are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Overview of Treatment Plan
Patients will start on cycle 1, day -7 with one week of ibrutinib monotherapy at the FDA-approved dose for CLL of 420 mg PO daily, which will allow time for mobilization of CLL cells from lymph nodes and marrow and will also allow for collection of patient samples for correlative studies. After the 1 week ibrutinib lead-in, FCR will subsequently be introduced on cycle 1, day 1, and administered at standard dosing for up to 6 cycles. Study visits will occur weekly in the first month, biweekly in the second and subsequently once per 28-day cycle. Disease assessments will be performed at baseline, after cycle 3, and 2 months after completing combination therapy, and will include CT scan and minimal residual disease (MRD) analysis on peripheral blood and bone marrow. Subjects who complete at least 3 cycles of FCR and subsequently need to discontinue FCR early for any reason including cytopenias will be permitted to continue on ibrutinib and will be followed per protocol as long as they do not receive other CLL therapy.

At the conclusion of the combination portion (up to 6 cycles), responders will be allowed to continue on ibrutinib maintenance for two years if they do not experience disease progression. During this 2 years of ibrutinib maintenance, patients will be followed with PB MRD testing every 6 months and with a BM MRD assessment at 1 year into maintenance. After 2 years of ibrutinib maintenance, all patients will undergo a repeat bone marrow biopsy. All those who are BM MRD-positive will continue on ibrutinib maintenance and will be monitored with PB MRD assessments every 6 months. All those who are BM MRD-negative will discontinue ibrutinib and will be followed with PB MRD assessments every 6 months. Those patients who remain PB MRD-negative will remain off ibrutinib. Patients who become PB MRD-positive will have repeat PB MRD testing 3 months later. If PB MRD-negative at that point they will remain off ibrutinib. If confirmed to be PB MRD positive on this second assessment they will resume ibrutinib and continue until progression or unacceptable toxicity. Also, if at any time a patient off ibrutinib has evidence of clinical CLL progression (as assessed by the treating investigator) they will resume ibrutinib at that time.

Of note, since patients in the original cohort of 35 patients were initially told that they would continue on ibrutinib maintenance until time of progression or unacceptable toxicity, such patients from part I who achieve BM MRD-negativity will be given a choice as to whether they will discontinue ibrutinib after 2 years of ibrutinib maintenance or whether they will continue on ibrutinib as previously planned. In contrast, patients recruited to the study in the new cohort who achieve BM MRD-negativity will be required to discontinue ibrutinib after 2 years of ibrutinib maintenance, but will be able to resume ibrutinib should they develop evidence of MRD-positivity at a subsequent time point.

Table 1. Overview of Study Agents

iFCR combination portion				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Ibrutinib	420 mg (three 140 mg capsules)	PO at approximately the same time each day	Daily starting d-7, then continuous during up to 6 cycles of chemotherapy, then maintenance	C1: 35 days (5 weeks) C2-6: 28 days (4 weeks)
Fludarabine	25 mg/m^2	IV over approximately 30 to 60 min., given before rituximab	Days 1-3, week 1	
Cyclophosphamide	250 mg/m^2	IV over approximately 30 to 60 min., given before rituximab	Days 1-3, week 1	
Rituximab	C1: 375 mg/m^2 C2-6: 500 mg/m^2	IV per institutional standard duration, given after FC	Day 1*, week 1	

**In cycle 1, rituximab dose may be split between day 1 (50 mg/m^2) and days 2 or 3 (325 mg/m^2) at the discretion of the treating investigator, as specified in the protocol section 5.2.3.*

Ibrutinib maintenance portion				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Ibrutinib	420 mg (three 140 mg capsules)	PO at same time each day	Daily	Continuous in monthly cycles, with discontinuation for patients achieving BM MRD-negativity after 2 years of ibrutinib maintenance

5.1 Pre-treatment Criteria

5.1.1 Cycle 1, Day -7

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.

5.1.2 Cycle 1, Day 1 and Day 1 of Subsequent Combination Therapy Cycles

- ANC must be ≥ 1000/mm3
- Platelet count must be ≥ 75K or ≥100% of baseline
  * If the platelet count is ≥ 25K but <75, patients may begin treatment on Day 1 of a cycle if their thrombocytopenia is attributed to bone marrow infiltration by CLL, as

documented by the investigator. Patients with platelet counts of <50,000 at the start of the cycle should have a follow-up platelet count 3 days into the cycle.

- All non-hematologic toxicities except for alopecia must have resolved to ≤ Grade 2, or to the patient's baseline condition

5.2 Agent Administration during combination therapy

In general, there is a +/- 4 day window for chemotherapy administration to allow for scheduling related issues. Chemoimmunotherapy dosing will be by institutional standard of care.

5.2.1 Fludarabine

Fludarabine (commercial supply from various manufacturers) will be administered prior to rituximab. Fludarabine will be dosed at 25 mg/m2 on days 1, 2, and 3 of each 28 day cycle. It will be administered IV over approximately 30 to 60 minutes per institutional routine. No pre-hydration or post-hydration is mandated. Anti-emetics will also be given per institutional routine. If patients experience Grade 1-3 infusion reactions with fludarabine administration, measures to prevent severe infusion reactions, including antihistamines, antipyretics and corticosteroids should be considered. Patients with grade 4 infusion reactions will be discontinued.

5.2.2 Cyclophosphamide

Cyclophosphamide (commercial supply from various manufacturers) will be administered prior to rituximab. Cyclophosphamide will be dosed at 250 mg/m2 on days 1, 2, and 3 of each 28 day cycle. It will be administered IV over approximately 30 to 60 minutes, per institutional routine. Pre-hydration with D5 ½ NS @ 500 mL/hr x 0.5 liters is recommended. Anti-emetics will also be given per institutional routine. If patients experience Grade 1-3 infusion reactions with cyclophosphamide administration, measures to prevent severe infusion reactions, including antihistamines, antipyretics and corticosteroids should be considered. Patients with grade 4 infusion reactions will be discontinued.

5.2.3 Rituximab

Rituximab will be administered after the chemotherapeutic agents. Rituximab from a commercial supply (Genentech, S. San Francisco, CA) will be administered IV at a dose of 375 mg/m2 on day 1 of cycle 1. Patients with ≥ 15,000 circulating malignant cells/ mm3 or at the discretion of the treating physician will receive only 50 mg/m2 on day 1 of cycle 1 to reduce the incidence of tumor lysis syndrome and infusion reactions, with the remaining 325 mg/m2 given on days 2 or 3 of cycle 1. If the day 1 infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day on day 2. For patients receiving split dose rituximab with cycle 1, if the day 2 or 3 infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day. Unless allergic, all patients should receive allopurinol for tumor lysis syndrome prophylaxis at least during the first cycle or as per standard of care.

In cycles 2-6, rituximab will be escalated to 500 mg/m2 and will be administered on day 1 of each remaining cycle. If the day 1 infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day on day 2. Patients with circulating disease ≥ 15,000 circulating malignant cells/mm3 or bulky disease may continue to receive allopurinol for prophylaxis of tumor lysis syndrome during cycles 2-6, at the discretion of the investigator.

Rituximab will be administered and hypersensitivity reactions will be treated per institutional guidelines.

5.2.4 Ibrutinib

Ibrutinib 420 mg will be administered orally once daily beginning on Day -7. The first dose of ibrutinib 420 mg (3 x 140-mg capsules) will be administered in the clinic on Day -7, and then self-administered by subjects at home on days -6, -5, -4, -3, -2, and -1. Ibrutinib will be administered in clinic on C1D1 just prior to administration of cycle 1 of FCR. 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.

Subjects completing at least 3 cycles of the combination portion of the trial who have achieved at least a PR will continue on to a maintenance portion of the trial with ibrutinib monotherapy given at 420 mg daily. Treatment will continue until disease progression, adverse event requiring discontinuation, subject withdrawal, or death. Patients who achieve BM-MRD negativity after 2 years of ibrutinib maintenance will discontinue ibrutinib but can resume at a later time should they become MRD-positive.

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.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 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 mandatory for all patients beginning with cycle 1. Neulasta should be administered at 6 mg SC x 1 on day 4 (or day 5 if necessary for scheduling reasons) of each cycle for up to 6 cycles Alternatively, Neupogen may be substituted at the discretion of the treating investigator and administered at a suggested dose of 300-480 mcg SC daily for up to 14 days, until ANC ≥ 1500 for two consecutive days. Granix may also be used, with dosing capped at 300 mcg and also may be discontinued when the ANC ≥1500 for two consecutive days. Neulasta, Neupogen, and Granix will be from commercial supply. If a patient is given white cell growth factor to self administer at home, documentation of adherence should be noted by the study team.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 receiving FCR chemotherapy, necessitating TLS prophylaxis including allopurinol and oral or IV hydration.

The risk of TLS is highest during the first cycle of therapy. It is recommended that allopurinol 300mg PO daily begin at least 3 days before the start of combination therapy and continue through the end of cycle 1or per standard of care. 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. To maintain fluid intake, subjects should be instructed to drink 8 to 10 eight ounce glasses of water each day for the first 14 days of Cycles 1 and 2. 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.

All subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix C) 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, Expected Toxicities and Dose Modifications, for additional instructions.

5.3.2 Treatment and Dose Modification for Tumor Lysis Syndrome

All subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix C) 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, and 6.4.1 Table 2, for additional instructions.

5.3.3 Prophylactic Antibiotics

Prophylaxis for Pneumocystis jiroveci pneumonia (PCP) with Bactrim or equivalent, and anti-herpetic viral prophylaxis with acyclovir or equivalent is mandatory during the trial. It is

recommended that prophylaxis be started at the initiation of the combination portion of therapy and should continue until the CD4 lymphocyte count is > 200.

5.3.4 Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib during procedures/surgeries (see Section 6.4). Supplements such as fish oil and vitamin E preparation should be avoided during treatment with ibrutinib.

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), should be monitored closely for signs and symptoms of bleeding and the risks and benefits of continuing ibrutinib treatment should be considered. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

5.3.5 Other Permitted Concomitant Medications

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

Usage of antimicrobial prophylaxis in accordance with standard practice (eg, ASCO guidelines [Flowers 2013]) is permitted and should be considered in subjects who are at increased risk for opportunistic infections.

Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) and transfusion is permitted in accordance with institutional policy (eg, ASCO guidelines [Smith 2006]).

In addition, short courses (≤30 days) of steroid treatment for non-cancer related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that are clinically indicated are permitted.

5.4 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression, and tolerance. In the absence of treatment-related adverse events or progressive disease, treatment may continue for up to 6 cycles of combination therapy with iFCR with subsequent ibrutinib monotherapy maintenance in responders until the time of progression, except in patients who

achieve BM MRD-negativity after 2 years of ibrutinib maintenance, who will discontinue ibrutinib. Such patients will continue to be followed on study even if they are off treatment.

Patients will be taken off study if any of the following occur:

- Disease progression as per IW-CLL criteria
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5 Duration of Follow Up

Participants will be followed every three months until subsequent therapy or until removal from study or death, whichever occurs first.

5.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Matthew Davids, M.D. at 617-632-3352, DFCI pager # 57215

Management and dose modifications associated with the above adverse events are outlined in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications).

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

6.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting in addition to routine reporting.

6.1.1 Adverse Event List for Fludarabine

The most common adverse reactions (frequency ≥10%) are edema, fever, fatigue, pain, chills, rash, nausea/vomiting, anorexia, diarrhea, gastrointestinal bleeding, urinary tract infection, neutropenia, febrile neutropenia, thrombocytopenia, anemia, leukopenia, weakness, myalgia, paresthesia, visual disturbance, cough, pneumonia, dyspnea, upper respiratory infection,

diaphoresis, infection. Rarely, fludarabine can be associated with autoimmune hemolytic anemia. Further details may be found in the FDA-approved label and Micromedex.

6.1.2 Adverse Event List for Cyclophosphamide

The most common adverse reactions (frequency ≥10%) are neutropenia, neutropenic fever, fever, thrombocytopenia, nausea, anemia, leukopenia, and vomiting. Other rare, but significant adverse events include hemorrhagic cystitis, alopecia, amenorrhea, oligospermia, and gonadal suppression. Further details may be found in the FDA-approved label and Micromedex.

6.1.3 Adverse Event List for Rituximab

Severe infusion reactions/hypersensitivity reactions: hypotension, angioedema, hypoxia or bronchospasm. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Additional AEs include fevers, renal toxicity, rash, neutropenia, infection including progressive multifocal leukoencephalopathy, hepatitis B reactivation, hypogammaglobulinemia, and tumor lysis syndrome. Further details may be found in the FDA-approved label and Micromedex.

6.1.4 Adverse Event List(s) for Ibrutinib

For a summary of the toxicology studies performed in animal models, please see section 2.3.2
For a detailed description of the toxicity profile of ibrutinib in clinical trials, please see section 2.4.2

6.2 Treatment-Related Lymphocytosis

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and investigator should be contacted.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/ small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and

typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (eg, >400,000/µL) has been observed in some subjects. Lymphocytosis was not commonly observed in subjects with Waldenström's macroglobulinemia treated with ibrutinib. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

6.3 Treatment of 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 experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11.4 for further information regarding AE reporting.
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.

6.4 Dose Modifications/Delays

Dose delays and modifications will be made using the recommendations below. Dose reductions to fludarabine and/or cyclophosphamide will be made as per section 6.4.2. Dose reductions of rituximab will not be permitted.

Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) 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. Non-hematologic Toxicity will be assessed using the NCI-CTCAE Version 4.0. Hematologic toxicity will be assessed by IWCLL 2008 criteria. 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 2 as suggested guidelines. There should be no attempt to make up for doses omitted due to toxicity.

Ibrutinib dosing may be withheld up to 4 weeks from the completion of a cycle (i.e. up to 8 weeks from the first dose of chemotherapy in a cycle), for toxicity. Ibrutinib doses withheld for > 4 weeks (>8 weeks from first dose of chemotherapy for a cycle) will result in discontinuation from the study. Any patient who requires > 2 dose reductions of the chemotherapy drugs due to toxicity over the course of the study will be discontinued from the study.

6.4.1 Ibrutinib dose modification

Dose reductions of ibrutinib during cycles 2-6 are permitted as per Table 2 if a toxicity is believed to be likely or definitely related to ibrutinib. After patients undergo their re-staging evaluation at the completion of the combination portion of the study and throughout the subsequent maintenance phase, dose reductions for ibrutinib may be made as per Table 2, based on the following criteria:

- Grade 4 ANC (<500/μL) for more than 7 days. The use of neutrophil growth factors is permitted per American Society of Clinical Oncology (ASCO) guidelines, and must be recorded in the case report form (CRF).

- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy; any other Grade 4 toxicity; any unmanageable Grade 3 toxicity.

Table 2. Ibrutinib Dose Reduction

Occurrence	Action to be taken
First	Withhold ibrutinib until recovery to ≤Grade 1 or baseline; may restart at original dose level
Second	Withhold ibrutinib until recovery to ≤Grade 1 or baseline; may restart at 1 dose level lower (280 mg per day)
Third	Withhold ibrutinib until recovery to ≤Grade 1 or baseline; may restart at 1 dose level lower (140 mg per day)
Fourth and beyond	Must discontinue ibrutinib unless Principal Investigator approves ongoing treatment

Dose changes must be recorded in the Dose Administration CRF.

- If platelets are < 20,000/ μL or < 50,000/μL in the presence of bleeding, ibrutinib must be held.

Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child- Pugh class B or C [See Appendix C]) are excluded from study participation. For subjects with existing chronic mild hepatic impairment (Child-Pugh class A) at enrollment, the starting dose has to be adjusted to a level of 280 mg daily (two capsules). For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines in section 6.4. Monitor subjects for signs of toxicity and follow dose modification guidance as needed.

Peri-operative dosing of ibrutinib

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied during the peri-operative 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 serosanguineous 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, or for at least 7 days after the urgent surgical procedure, whichever is longer.

6.4.2 FCR dose reduction

Dose reductions due to toxicity from FCR will be made according to standard practice. For example, patients may have a 20% dose reduction of fludarabine from 25 mg/m^2 to 20 mg/m^2 and cyclophosphamide from 250 mg/m^2 to 200 mg/m^2. Further dose reductions can be made to fludarabine 15 mg/m^2 and cyclophosphamide 150 mg/m^2, but should be discussed with the PI. Dose reductions to rituximab will not be permitted.

For patients with a creatinine of > 1.5, fludarabine should be dose-reduced to 20 mg/m^2. Patients whose creatinine improves to ≤ 1.5 may receive full dose fludarabine in future cycles.

6.5 Study Discontinuation

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

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Fludarabine, Cyclophosphamide, Rituximab (FCR)

7.1.1 **Fludarabine**

Identification and Mechanism of Action – Fludarabine is a nucleoside analog. It is metabolized to 2-fluoro-ara-ATP whereby it inhibits DNA synthesis through inhibition of DNA polymerase, ribonucleotide reductase, and DNA primase.

Relevant FDA Indications – Upfront and relapsed CLL

Non-FDA Labeled Indications – AML, malignant lymphoma, membranous glomerulonephritis, mycosis fungoides, Sezary's disease.

Dose and Schedule – 25 mg/m2/day, days 1-3, every 28 days.

How Supplied – 50 mg vials of powder (solution is also acceptable) to be diluted in 100 ml to 125 ml of D5W or NS for intravenous infusion over approximately 30 to 60 minutes. Fludarabine will be commercially supplied and is available from various manufacturers.

7.1.2 **Cyclophosphamide**

Identification and Mechanism of Action – Cyclophosphamide is an alkylating agent that prevents cell division by cross-linking DNA strands and decreasing DNA synthesis. It is a cell cycle phase nonspecific agent. Cyclophosphamide also possesses potent immunosuppressive activity. Cyclophosphamide is a prodrug that must be metabolized to active metabolites in the liver.

Relevant FDA Indications – Upfront and relapsed CLL

Non-FDA Labeled Indications – Ewing's sarcoma, rhabdomyosarcoma, Wilms tumor, ovarian germ cell tumors, gestational trophoblastic tumors, small cell lung cancer, testicular cancer, pheochromocytoma, hematopoietic stem cell transplant conditioning..

Dose and Schedule – 250 mg/m2/day, days 1-3, every 28 days.

How Supplied – 500 mg (1 ea), 1 g (1 ea), 2 g (1 ea) solution, reconstituted for intravenous infusion over approximately 30 to 60 minutes. Cyclophosphamide will be commercially supplied and is available from various manufacturers.

7.1.3 **Rituximab**

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL)

or 500 mg (50 mL) single-use vials. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

Reconstitution
Use appropriate aseptic technique. Withdraw the necessary amount of Rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 12 hours. No incompatibilities between Rituximab and polyvinylchloride or polyethylene bags have been observed.

Stability and Storage
Rituximab vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. Rituximab vials should be protected from direct sunlight.

Dosage and Administration
Rituximab will be administered IV at a dose of 375 mg/m2 on day 1 of cycle 1.
Patients with ≥ 15,000 circulating malignant cells/ mm3 or at the discretion of the treating physician will receive only 50 mg/m2 on day 1 of cycle 1 to reduce the incidence of tumor lysis syndrome and infusion reactions, with the remaining 325 mg/m^2 given on day 2 or 3 of cycle 1. If the day 1 infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day on day 2. For patients receiving split dose rituximab with cycle 1, if the day 2 or 3 infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day. In cycles 2-6, rituximab will be escalated to 500 mg/m^2 and will be administered on day 1 of each cycle. If the day 1 infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day on day 2. Rituximab may be administered in an outpatient setting and will be administered according to standard clinical practice, roughly described below.

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Hypersensitivity reactions may occur. Standard premedication, usually consisting of acetaminophen 650-1000 mg po x 1, hydrocortisone 100 mg IV x 1 (or any equivalent corticosteroid like methylprednisolone or dexamethasone), and diphenhydramine 25-50 mg IV or po x 1, should be given before each infusion of rituximab.

Rituximab for patients with starting absolute lymphocyte count < 15,000 / μl:
First Infusion: The Rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. Variations consistent with standard administration of rituximab are acceptable per institutional guidelines.

Rituximab infusion should be interrupted for severe reactions. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen and corticosteroids if needed is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Most patients who have experienced nonlife-threatening infusion-related reactions have been able to complete the full course of rituximab therapy. Epinephrine, antihistamines and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to Rituximab (e.g., anaphylaxis). If the day 1 infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day on day 2. Subsequent Infusions: Subsequent Rituximab infusions can be administered with 20 percent of the total dose over 30 minutes, followed by the remaining 80 percent of the total dose over 60 minutes.

Rituximab for patients with absolute lymphocyte count >15,000 / μl or those patients with large tumor burden (at the discretion of the treating physician):

First cycle only: On day 1, patients will receive rituximab 50 mg/m^2 IV over 4 hours without rate escalation, following chemotherapy administration. On day 2 or 3, patients may receive rituximab 325 mg/m^2 IV starting at 50 mg/hr, escalating by 50 mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr as tolerated, with slight variations permitted according to standard protocol per institutional standards. If the day 2 or 3 infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day.

Second and subsequent cycles: Rituximab 500 mg/m^2: IV on day 1 according to standard protocol. If the day 1 infusion cannot be completed within 1 day, the patient is allowed to receive the remainder of the infusion the following day on day 2.

Procurement
Rituximab is approved by the FDA for treatment of low-grade B cell lymphomas and is widely used for the treatment of chronic lymphocytic leukemia. Rituximab for this study will be from commercial supply, manufactured by Genentech (South San Francisco, CA).

7.2 Ibrutinib

7.2.1 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 delivered in the clinic, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to patients in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated (using form approved by the institutional) at each visit. Returned capsules must not be redispensed to anyone.

Remaining unused study drug supply will be destroyed at the clinical site; standard institutional policy should be followed. Records documenting the date of study drug destruction, relevant lot numbers, and destroyed should be maintained.

7.2.2 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 pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

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

7.2.3 Storage and Stability

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

7.2.4 Compatibility

Not applicable

7.2.5 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.

7.2.6 Availability

Ibrutinib is an investigational agent and will be supplied free-of-charge from Pharmacyclics, LLC, Sunnyvale, CA.

7.2.7 Preparation

Ibrutinib will be provided by Pharmacyclics in capsule form, and final packaging and labeling will be performed as per standard practices at the outpatient pharmacy of the DF/HCC institution treating the patient.

7.2.8 Administration

Ibrutinib is administered orally as a capsule formulation daily in 28 day cycles (except for cycle 1, 35 days) as a fixed dose in mg, and should be administered using the minimal number of capsules necessary.

Beginning on Cycle 1, Day -7, ibrutinib will be administered orally daily at 420 mg, and will be administered in 28 day cycles (except for cycle 1, which is 35 days). 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. 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. 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.

7.2.9 Ordering

The site's pharmacy will order ibrutinib directly from Pharmacyclics LLC, Sunnyvale, CA, who will be providing the study drug free of charge. Under certain circumstances, ibrutinib may be shipped to the patient's residence after prospective approval of the overall principal investigator.

7.2.10 Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of ibrutinib using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

7.2.11 Destruction and Return

All unused ibrutinib will be retained at the site. After full drug accountability and reconciliation, the Investigators will return all ibrutinib to Pharmacyclics, or its designee or, at Pharmacyclics' request, will dispose of the study drug at the clinical trial site, according to site procedures. Destruction will be documented in the Drug Accountability Record Form. If any study drug is lost or damaged, the disposition of the study drug should be documented.

Patients should be instructed to bring all unused ibrutinib to each study visit. The study site should count all capsules that the patient returns, and should take account for taken doses, missed doses, doses reduced due to missing or lost capsules, etc., before dispensing new study drug to the patient. Any patient who does not take the prescribed dose should be requested to return the remaining drug to the clinical trial site for accountability.

7.2.12 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 experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11.4 for further information regarding AE reporting.

8. CORRELATIVE/SPECIAL STUDIES

All sites will be encouraged to provide the correlative samples for analysis, as feasible. While the goal of the biomarkers 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 or strategic 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.

8.1 Pharmacokinetic Studies (Dana Farber/Harvard Cancer Center Only)

A limited number of pharmacokinetics samples will be obtained to confirm in this previously untreated CLL population the PK data previously obtained in the relapsed/refractory population and to evaluate PK of ibrutinib in combination with FCR.

Blood samples for pharmacokinetic evaluations will be drawn on Cycle 1, day -7 predose and day 1 of treatment at following time-points: predose and at 1, 2, 4, and 6 hours after taking ibrutinib. On days that PK samples are taken, ibrutinib should be taken in clinic. Ibrutinib and metabolite concentrations will be used for analysis of PK parameters that may include: Cmax, half-life, exposure (AUC).

Pharmacokinetic samples will be drawn on **DF/HCC patients only.**

8.1.1 Handling of Specimens(s)

USE 1 x 2-mL GREEN TOP SODIUM HEPARIN TUBE FOR EACH PK COLLECTION.

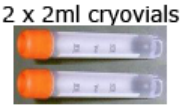
1. Allow tube to fill COMPLETELY, as far as the vacuum will allow.
2. Mix the tube immediately upon completion to avoid clotting by inverting gently 5 times. DO NOT SHAKE.
3. Place the blood samples on melting ice until centrifugation
4. Place the sample in a refrigerated centrifuge (0-4°C).

NOTE: When necessary use a refrigerated centrifuge bucket in cases where a refrigerated centrifuge is not available. Maintain cold temperature during the plasma preparation process.

5. Centrifuge tube within 60 minutes of collection at 4°C for 15 minutes at 2500 rpm.
6. Transfer plasma with pipette equally into two 2-mL cryovials (approximately 0.5 mL of plasma in each tube).
7. Enter the Subject ID number on the sample labels.
8. Store plasma samples in a freezer at -80°C or below, within approximately 60 minutes of blood collection.
9. Ship samples **FROZEN** to **Frontage Laboratories**

NOTE: Every effort should be made to collect the full 2 mL blood sample at each time point. In the event that less than 1 mL of blood is collected, the sample will be processed as described above except that the plasma will not be divided into two tubes. All deviations will be recorded on the PK worksheet. This single plasma sample should be frozen, stored and shipped with the primary set of samples.

All PK Timepoints

TEST	COLLECT	PREPARE	CONTAINER	SHIP TEMP
PK	1 x 2ml Green Sodium Heparin 	Centrifuge & Transfer Plasma	2 x 2ml cryovials 	**Frozen**

8.1.2 Shipping of Specimen(s)

PK SPECIMENS to be batch shipped (FROZEN) after collection from each subject. Please include:

- One primary set of samples for each subject
- One back-up set of samples for each subject (unless only single sample available)

Samples should be shipped on dry ice **Monday through Thursday** only.

As much as possible, a complete set of **primary** samples (all time points) for a subject should be batched and shipped together in the same shipment.

Ship the back-up set after the confirmation of receipt of the primary set by Frontage Laboratories, Inc.

Do **NOT** ship back-up aliquots of samples in the same shipment as the primary samples from the same subject.

Contact FEDEX customer service to determine the latest pickup time for your site and the scheduling deadline. Record the FEDEX Tracking number from the top of each airbill for your records and tracking purposes.

Note: A Shipping Notification fax should be send prior to shipping.
Electronic packaging slip must be sent to jscott@frontagelab.com and mhong@frontagelab.com

SHIPPING ADDRESS:

Jessica Scott
Sample Coordinator
Frontage Laboratories, Inc.
700 Pennsylvania Drive
Exton, PA 19341
P: 484-348-4790
F: 610-232-0101

8.2 Pharmacodynamic Studies

8.2.1 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 iFCR 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 ibrutinib monotherapy on cycle 1 day 1 (prior to receiving chemotherapy), 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 as a single agent. We will also attempt to identify potential resistance mechanisms by looking at whether patients who do not achieve an MRD-negative CR have different upfront BH3 profiles from those who do. Finally, another tube 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 or Dr. Matthew Davids, where they will undergo Ficoll purification and then be viably frozen in FBS with 10% DMSO. All viably-frozen samples will be batched and transported to the laboratory of Dr. Matthew Davids, where the BH3 profiling assays will be performed (for detailed methods see Ryan et al., 2010).

SHIPPING ADDRESS:
Timothy Lehmberg, Research Technician

Davids Laboratory
Dana Farber Cancer Institute
450 Brookline Ave, Mayer 545
Boston, MA 02215, U.S.A.
617-632-5847 (phone)

8.2.2 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.

8.2.3 Pharmacodynamic Markers

Pharmacodynamic markers will also be assessed to determine whether ibrutinib is hitting its proposed target *in vivo*. Peripheral blood samples will be drawn pretreatment on cycle 1, day 1, at the end of cycle 3, at the end of combination therapy, 6 months after the end of combination therapy, and 12 months after the end of combination therapy. Additional peripheral blood samples are requested every subsequent 6 months for up to 5 additional time points. These samples will be brought to the laboratory of Dr. Jennifer Brown, where PBMCs will be isolated for analysis. Viably frozen cells will be shipped to Pharmacyclics, who will use phosphoflow cytometry to determine the levels of phospho-AKT, phosphor-ERK, and phospho-BTK compared to total AKT, ERK, and BTK, respectively. These analyses may be confirmed in a subset of patients by Western Blot. In addition, current work has suggested that reduction in the cell proliferation marker Ki-67 in peripheral blood CLL cells occurs rapidly in patients treated with BCR pathway antagonists, and this may also be assessed in the Brown lab by phosphoflow cytometry in samples from patients on our study.

8.2.4 Adaptive Sequencing Studies

Peripheral blood and/or bone marrow samples will 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. The collection kits and shipping supplies will be provided to the sites by Adaptive. These samples will be packaged whole, and shipped to Adaptive in Seattle, WA same day priority overnight. Using Adaptive's ClonoSEQ 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. Adaptive MRD levels will be quantified using spiked-in reference sequences.

8.2.5 Minimal Residual Disease

Bone marrow samples will be collected for minimal residual disease analysis by Integrated Oncology by flow cytometry at the end of cycle 3, the re-staging evaluation approximately 2 months after the end of combination therapy with FCR, and again approximately 12 and 24 months after combination therapy unless found to be MRD negative in the marrow at the 2 months post FCR visit. As this is a standard of care test, patient's insurance will be billed for disease monitoring.

Blood samples will be collected for minimal residual disease analysis by Integrated Oncology by flow cytometry at the following time points: end of Cycle 3, 2 months after end of combination therapy with FCR, 6 months after end of combination therapy with FCR, approximately 12, 18, and 24 months post FCR and approximately every 6 months/cycles thereafter.

Patients who have not already had Zap70, *TP53* and *IGHV* testing will send additional baseline samples to Integrated Oncology. These samples will be shipped alongside the Integrated Oncology/LabCorp requisition form ambient priority overnight to:

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

**Please refer to the sample collection table below for detailed sample collection time points

8.2.6 Sample Collection Schedule – All Sites

Sample Time Point	Container[1]	Sample Type	Shipping Method	Recipient[3]
Screening or Pre-dose Day -7	6x 6mL Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
	1x6ml Green Top	Bone Marrow Aspirate		
	1x Oragene Kit	Saliva[2]	Ambient overnight	
	1x10ml EDTA	Peripheral Blood	Via kit overnight	Adaptive
	1x3ml EDTA	Bone Marrow Aspirate		
	2x10ml Purple Top* 1x6ml Green Top*	Peripheral Blood	Ambient overnight	Integrated Oncology/LabCorp
Cycle 1 Day 1 (Prior to chemotherapy)	6x6mL Green Top 1x6ml Red Top	Peripheral blood	Fridge pack overnight	CLL Center, J. Brown lab
End of Cycle 3[2]	6x6ml Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	CLL Center J. Brown lab
	1x6ml Green Top	Bone Marrow Aspirate		
	1x 6ml Green Top	Bone Marrow Aspirate	Ambient overnight	Integrated Oncology/LabCorp
	1x6ml Green Top	Peripheral Blood		
Re-Staging (2 months post FCR)	6x6mL Green Top 1x6mL Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
	1x6ml Green Top	Bone Marrow Aspirate		
	1x10ml Purple	Peripheral Blood	Via kit overnight	Adaptive
	1x3ml Purple	Bone Marrow Aspirate		
	1x 6ml Green Top	Bone Marrow Aspirate	Ambient overnight	Integrated Oncology/LabCorp
6 Months post FCR	1x6ml Green Top	Peripheral Blood	Ambient overnight	Integrated OncologyLabCorp
	6x6mL Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
12 months post FCR	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	Bone Marrow Aspirate	Ambient overnight	Integrated Oncology/LabCorp
	1x6ml Green Top	Peripheral Blood		
18 months post FCR	6x6mL Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
	1x6ml Green Top	Peripheral Blood	Ambient overnight	Integrated Oncology/LabCorp
24 months post FCR	6x6mL Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	Integrated Oncology/LabCorp
	1x6ml Green top	Bone Marrow Aspirate		

	1x6ml Green Top	Bone Marrow Aspirate	Ambient overnight	CLL Center, J. Brown lab
	1x6ml Green Top	Peripheral Blood		
30 months post FCR	1x6ml Green Top	Peripheral Blood	Ambient overnight	Genzyme/LabCorp
	2x6mL Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
36 months post FCR	1x6ml Green Top	Peripheral Blood	Ambient overnight	Integrated Oncology/LabCorp
	1x6ml Green Top	Bone Marrow Aspirate		
	2x6mL Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
42 months post FCR	1x6ml Green Top	Peripheral Blood	Ambient overnight	Integrated Oncology/LabCorp
	2x6mL Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
48 months post FCR**	1x6ml Green Top 1x6ml Green Top	Peripheral Blood Bone Marrow Aspirate	Ambient overnight	Integrated Oncology/LabCorp
	2x6mL Green Top 1x6ml Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
Relapse/Disease Progression	6x6mL Green Top 1x6mL Red Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
	1x6ml Green Top	Bone Marrow Aspirate		

[1] Green top= sodium heparin tube; Red top= no additive; Purple top: K2EDTA
[2]Oragene kits will be provided by the lead site, and requires approximately 2mLs of saliva and can be obtained at any time during the trial
[3]Sequenta provides collection kits and shipping supplies; LabCorp and CLL labs only provides requisition form* Samples required for all patients at baseline unless already been tested for Zap70, *IGHV* and *TP53*
** MRD on blood should be done q6 months for all patients- Bone marrow should be done yearly for those that remain MRD positive in the marrow

8.2.7 Sample Collection Schedule- Cycle 1, Day-7 Pharmacokinetics: DF/HCC Only

Sample Time Point[1]	**Container[2]**	**Sample Type**	**Shipping Method**	**Recipient[3,4]**
Pre Ibrutinib Day -7	1x2mL Green Top	Peripheral Blood	Batch ship frozen	Frontage Lab
Pre-Ibrutinib Day1[5]	1x2mL Green Top	Peripheral Blood	Batch ship frozen	Frontage Lab
1 Hr Post Ibrutinib	1x2mL Green Top	Peripheral Blood	Batch ship frozen	Frontage Lab
2 Hrs Post Ibrutinib	1x2mL Green Top	Peripheral Blood	Batch ship frozen	Frontage Lab
4 Hrs Post Ibrutinib	1x2mL Green Top	Peripheral Blood	Batch ship frozen	Frontage Lab
6 Hrs Post Ibrutinib	1x2mL Green Top	Peripheral Blood	Batch ship frozen	Frontage Lab

[1] All PK samples should be drawn within 10 minutes of specified time point.
[2]Green top= heparinized tube
[3] Shipping Address: Jessica Scott, Sample Coordinator, Frontage Laboratories, Inc., 700 Pennsylvania Drive Exton, PA 19341

[4]Ship primary set of cryovials frozen after all PKs are complete and processed into cryovials on dry ice via Fed-Ex overnight using site's materials. Only send second set of cryovials once first set has been received and confirmed by Frontage Labs.
[5] Day 1 corresponds to the start of FCR therapy after 7 day lead in dosing of ibrutinib. Samples must be drawn pre-chemotherapy.

9. STUDY CALENDAR

Baseline evaluations are generally to be conducted within 2 weeks prior to start of protocol therapy. Scans must be done ≤4 weeks prior to the start of therapy. Bone marrow biopsy should be done ≤4 weeks prior to the start of therapy unless done within the prior 3 months. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Subjects must meet eligibility criteria to start therapy on C1D-7.

All assessments must be performed prior to administration of any study medication. All study assessments should be performed within ±7 days of the protocol-specified date, unless otherwise noted. All study visits should occur within a ±4 day window, except for visits occurring during the maintenance and follow-up phases after the completion of the combination portion of the study, which may occur within a ±14 day window. For patients who have discontinued ibrutinib and remain on study, a ±21 day window is permitted.

9.1 Pre-Treatment Evaluations

- Signed informed consent document
- Vital signs and physical examination
- Medical history: Detailed documentation of disease and treatment history with outcomes
- ECOG performance status
- Concurrent medical conditions
- Concurrent medications
- CBC with differential and platelet count
- Serum chemistries: Electrolytes (sodium, potassium, chloride, and bicarbonate),
- calcium, magnesium, phosphate, blood urea nitrogen (BUN), creatinine, glucose, uric acid, lactate dehydrogenase (LDH), and liver function tests (aspartate
- aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase
- (ALP), total protein, albumin, total bilirubin, direct bilirubin, lipase
- Coagulation studies including prothrombin time and partial thromboplastin time
- Thyroid stimulating hormone level (TSH)
- Urinalysis
- Quantitative immunoglobulins and serum protein electrophoresis and beta 2 microglobulin
- Direct antiglobulin test (Direct Coombs' test)
- Reticulocyte count
- Bone marrow biopsy, including core biopsy, aspirate, flow cytometry (lymphoma panel), karyotype, and FISH (CLL panel)
    - Patients who have had prognostic assessments (CLL FISH panel) performed within 6 months prior to registration do not need to have this assessment repeated
- CD4 panel (routine T-cell subsets)

- Hepatitis B ,C, and HIV serologies: HBV surface antigen, HBV surface antibody, HBV core antibody: if HBV core antibody is positive, must have a negative HBV viral load to enroll. HCV antibody: if positive, must have negative HCV viral load to enroll. HIV 1/2 antibody: must have negative result to enroll)
- Serum pregnancy test for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). A tubal ligation is adequate documentation that a patient is not of child bearing potential.
- Baseline EKG
- Full body CT scan (neck, chest, abdomen/pelvis) with oral and IV contrast, unless
- contrast is contraindicated, in which case alternative imaging options can be discussed with the principal investigator. Measurements will be made by the DF/HCC tumor imaging metric core (TIMC).
- Bone marrow biopsy must be done ≤4 weeks prior to the start of therapy unless done within the prior 3 months without intervening therapy
- Serum *IGHV* and *TP53* mutational analysis (1 purple top 10 cc tube each) and ZAP-70 testing (1 green top 6 cc tube)-
    - Test performed by Genzyme/LabCorp; see correlatives 8.2.1.6 - Patients who have had prognostic assessments (*TP53, IGHV*, or Zap70) performed within 6 months prior to registration do not need to have these assessments repeated
      **IGHV* does not need to be repeated if previously tested and source verifiable

9.2 Evaluations During Combination Treatment

9.2.1 The following assessments will be performed weekly during the first cycle (including Cycle 1 Day 2 and Cycle 1 Day 3), every 2 weeks during the second cycle, and on day 1 of all subsequent combination cycles:

Physical Examination

- Recording of AEs (patients and/or family members will be instructed to telephone the site with any changes in mental or physical status or with any questions regarding treatment)
- CBC with differential and platelet count
- Serum chemistries: Electrolytes (sodium, potassium, chloride, and bicarbonate), calcium, magnesium, phosphate, blood urea nitrogen (BUN), creatinine, glucose, uric acid, lactate dehydrogenase (LDH), and liver function tests (aspartate aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein, albumin, total bilirubin, direct bilirubin.

9.2.2 The following assessments will be performed only on day 1 of all cycles:

- ECOG Performance Status
- Recording of concomitant medications.

9.2.3 The following objective disease efficacy assessments are to be performed within 7 days prior to completing cycles 3 (or pretreatment on cycle 4 day 1) and one month after completion of cycle 6 (or the final cycle of FCR if fewer than 6 cycles are given, i.e. 2 months after last dose of chemotherapy):

- Full body CT scan (neck, chest, abdomen/pelvis) with oral and IV contrast, unless contrast is contraindicated, in which case alternative imaging options can be discussed with the principal investigator. Measurements will be made by the DF/HCC tumor imaging metric core (TIMC).
- Bone Marrow Biopsy including core biopsy, aspirate, and FISH (CLL panel)
- Minimal Residual Disease (MRD) assessment will be made by flow cytometry both on bone marrow as well as peripheral blood sent to Integrated Oncology. Please refer to Section 8.2.6 for specific MRD testing time points

9.3 Evaluations after iFCR Treatment

For patients completing 6 cycles of therapy, restaging assessments should occur 1 month after completing cycle 6 (i.e. 2 months after last dose of chemotherapy). When a patient discontinues treatment prior to completion of cycle 6, end of study assessments are to be performed approximately 8 weeks after the last dose of chemotherapy. If the patient is not able to undergo final re-staging, the reason for not completing the end of study assessments must be recorded in the patient's source documents.

The following clinical assessments will be performed:

- Full physical examination
- Weight and vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- ECOG Performance Status
- Recording of AEs
- Recording of concomitant medications
- Full body CT scan (neck, chest, abdomen/pelvis) with oral and IV contrast, unless contrast is contraindicated, in which case alternative imaging options can be discussed with the principal investigator. Measurements will be made by the DF/HCC tumor imaging metric core (TIMC). De-identified scans will be sent to the lead site for submission to TIMC for analysis.

The following laboratory assessments will be performed:

- CBC with differential and platelet count
- Serum chemistries: Na, K, Cl, HCO3, glucose, blood urea nitrogen (BUN), creatinine, calcium, magnesium, phosphate, total bilirubin, AST, ALT, alkaline phosphatase, albumin, and total protein
- Bone Marrow Biopsy including CLL FISH panel in patients
- completing the chemotherapy portion of the study, for end-of-treatment response assessment (to be completed 4 weeks following completion of the

final cycle of chemotherapy, i.e. 8 weeks after the last dose of chemotherapy).

- Minimal Residual Disease (MRD) assessment will be made by flow cytometry both on bone marrow as well as peripheral blood sent to Integrated Oncology. Please refer to Section 8.2.6 for specific MRD testing time points

9.3.1 Ibrutinib Maintenance

Patients who complete the combination portion of iFCR and have achieved a PR, nPR, CRi, or CR (regardless of MRD status) will be eligible to proceed with ibrutinib monotherapy as maintenance, and will continue at the same dose they were previously on during the combination portion of the trial.

All patients who go on to receive ibrutinib maintenance will be followed with visits every 2 months until the 1 year mark and every three months thereafter until time of progression, AE leading to discontinuation, withdrawal of consent, or death.

At the conclusion of the combination portion (up to 6 cycles), responders will be allowed to continue on ibrutinib maintenance for two years if they do not experience disease progression. During this 2 years of ibrutinib maintenance, patients will be followed with PB MRD testing every 6 months and with a BM MRD assessment at 1 year into maintenance. After 2 years of ibrutinib maintenance, all patients will undergo a repeat bone marrow biopsy. All those who are BM MRD-positive will continue on ibrutinib maintenance and will be monitored with PB MRD assessments every 6 months. . All those who are BM MRD-negative will discontinue ibrutinib and will be followed with PB MRD assessments every 6 months. Those patients who remain PB MRD-negative will remain off ibrutinib. Patients who become PB MRD-positive will have repeat PB MRD testing 3 months later. If PB MRD-negative at that point they will remain off ibrutinib. If confirmed to be PB MRD positive on this second assessment they will resume ibrutinib and continue until progression or unacceptable toxicity. Also, if at any time a patient off ibrutinib has evidence of clinical CLL progression (as assessed by the treating investigator) they will resume ibrutinib at that time.

The following clinical assessments will be performed:

- History
- Full physical examination
- Weight and vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- ECOG Performance Status
- Recording of AEs
- Recording of concomitant medications
- Re-staging with full body CT is required for patients in partial remission every 6 months or until complete remission is achieved. Re-staging scans are also required for patients on ibrutinib who are coming off study due to clinical or laboratory disease progression. Routine re-staging CT scan is not required for patients in complete remission, and may be performed at the discretion of the treating investigator. When employed, the recommended schedule in

remission is every 6 months beginning 6 months following the end of treatment and continued until disease progression

- For patients in radiographic CR or CRi who have not achieved bone marrow MRD-negativity, serial bone marrow biopsies to assess MRD status will be performed at yearly intervals and MRD status checked on peripheral blood at 3 month intervals until MRD-negativity in both compartments is achieved. This will be done by Integrated Oncology. Please refer to Section 8.2.6 for specific MRD testing time points
- For patients who have achieved MRD-negativity in the blood, serial MRD testing by flow cytometry will be performed every 6 months in the peripheral blood by Integrated Oncology. Please refer to Section 8.2.6 for specific MRD testing time points

9.3.2 Patients who do not receive ibrutinib maintenance

Patients who do not go on to receive ibrutinib maintenance due to not achieving a clinical response to iFCR or due to patient preference will be followed until initiation of new therapy, or death.

The following procedures will be completed:

- Recording of AEs (patients and/or family members will be instructed to telephone the site with any changes in mental or physical status) for 90 days following their last dose of ibrutinib

- Restaging with full body CT is optional for patients in complete remission, and may be performed at the discretion of the treating investigator. When employed, the recommended schedule in remission is every 6 months beginning 6 months following the end of treatment and continued until disease progression

Study Calendar	Pre-Study[l]	C1D-7	C1D1	C1D2 C1D3	C1D8	C1D15	C1D22	C2D1	C2D15	C3-6D1	1 month post FCR	2 months post FCR (re-staging)	Maintenance[m] (q 2 mo up to 1 yr, then q3 mo)	Off Treat-ment[c]
Ibrutinib		X----------											----------X	
FCR [i]			X	X				X		X				
Consent	X													
History	X	X	X		X	X	X	X	X	X	X	X	X	X
Con meds	X----------												----------X	
Physical exam	X	X	X		X	X	X	X	X	X	X	X	X	X
Performance Status	X	X	X		X	X	X	X	X	X	X	X	X	X
CBC w/diff	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
B-HCG [b]	X[b]													
EKG	X													
Marrow Biopsy [d]	X									X		X	X	
MRD eval [e]										X		X	X	
Radiographic evaluation [f]	X									X		X	X	
Correlatives	X		X									X[g]	X	X[h]
Adaptive	X[g]											X		
PK studies		X[k]	X[k]											
AE eval	X----------													----------X

a: Serum chemistry: albumin, alkaline phosphatase, total bilirubin, BUN, creatinine, calcium, chloride, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium- Please refer to 9.2 for more information on labs required for screening, C1D2 and C1D3.
b: Serum pregnancy test (women of childbearing potential).
c: Off-study evaluation should be conducted at DFCI, except in case of extenuating circumstances.
d: Bone marrow biopsy is performed at screening, just prior to starting cycle 4 , 2 months post FCR re-staging visit, and then yearly in patients on maintenance who achieve CR but remain MRD positive in the bone marrow. Patients who are MRD positive in the peripheral blood at the completion of the FCR portion of the study and subsequently become MRD negative in the peripheral blood should also have a bone marrow biopsy performed to evaluate for conversion to MRD negativity in the bone marrow.
e: MRD assessments will be performed by Integrated Oncology on both bone marrow and blood just prior to starting cycle 4, at the re-staging visit after completing FCR (2 months post FCR), and then on maintenance in the blood every 6 months and in the bone marrow once per year in patients who remain MRD –positive in the bone marrow -For full MRD testing schedule, please refer to Section 8.2.6
f: Radiographic evaluations include CT neck/chest/abdomen/pelvis, and will occur at screening, at the pre-cycle 4 re-staging visit, and at the re-staging visit 2 months after completing FCR. Additional radiographic evaluation during the maintenance phase is not required, but is recommended to be performed at q6 month intervals
g: Adaptive samples drawn only pre-treatment and at re-staging visit 2 months after completing combination therapy (FCR)
h: For patients coming off study due to disease progression
i: To be given as per standard of care, with FCR on day 1, FC on days 2 and 3, and an option to split the Rituxan dose between different days, as outlined in section 5 of the protocol.
k: PK samples will be collected on Day -7 for ibrutinib exposure after ibrutinib administration alone and on Day 1 for steady-state ibrutinib exposure after before and after FCR (DF/HCC Only)
l. Screening labs are per section 9.1
m. After 2 years of ibrutinib maintenance, all patients will undergo a repeat bone marrow biopsy. All those who are BM MRD-positive will continue on ibrutinib maintenance and will be monitored with PB MRD assessments every 6 months. All those who are BM MRD-negative will discontinue ibrutinib and will be followed with PB MRD assessments every 6 months. Those patients who remain PB MRD-negative will remain off ibrutinib. Patients who become PB MRD-positive will have repeat PB MRD testing 3 months later. If PB MRD-negative at that point they will remain off ibrutinib. If confirmed to be PB MRD positive on this second assessment they will resume ibrutinib and continue until progression or unacceptable toxicity. Also, if at any time a patient off ibrutinib has evidence of clinical CLL progression (as assessed by the treating investigator) they will resume ibrutinib at that time.

10. MEASUREMENT OF EFFECT

10.1 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 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.)

10.2 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 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination 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.

10.3 Response Criteria

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

10.3.1 Complete remission (CR):

CR requires all of the following criteria:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 x 10^9/L (4000/μL). 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 x 10^9/L (1,500/μL) without need for exogenous growth factors, Platelets more than 100 x 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.

10.3.2 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.

10.3.3 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.

10.3.4 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 x 10^9/L (1,500/μL) without need for exogenous growth factors, Platelet counts greater than 100 x 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.

10.3.5 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.

10.3.6 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 x 10^9/L (100 000/µL), which occurs at least 3 months after treatment, defines disease progression, if marrow biopsy demonstrates an infiltrate of clonal CLL cells.

10.3.7 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.

10.3.8 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.

10.3.9 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.

10.4 Response Review

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

11. ADVERSE EVENT REPORTING REQUIREMENTS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug.

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

Disease progression is not an adverse event; rather it may be the cause of an adverse event. The clinical diagnosis that is associated with disease progression must be reported as all other adverse events. "Disease progression" should never be used as an adverse event term.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.
- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL/SLL that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

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

chemotherapy, or due to long travel distances are also not SAEs.

Diagnostic Testing and Procedures: Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

11.1.2 Serious adverse event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the drug manufacturer believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient or patient may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the Investigator's perspective may be informed by having actually observed the event, and the drug manufacturer is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the drug manufacturer or the Investigator believes that the event is serious, the event will be considered serious.

11.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agents.

11.1.3.2 Unexpected adverse event

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

11.1.4 Attribution

The Principal Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

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

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant’s medical record and on the appropriate study-specific case report forms.

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE.

Should a patient experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

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

A copy of the CTCAE version 4.03 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.3 Reporting Requirements

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

11.4 Reporting to the Study Sponsor

11.4.1 Serious 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.

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 toxicities, and grade 5 (death) regardless of study phase or attribution.

11.4.2 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.

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE 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 Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days[#]	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	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. **See section 11.4.3**					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

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

In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Matthew Davids, MD
617-632-6331 (phone)
Matthew_Davids@dfci.harvard.edu
617-582-9104 (fax)

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

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

11.4.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. entered in the InForm case report form).

CTCAE Category	Adverse Event	Grade	Hospitalization or Prolongation of Hospitalization	Attribution
Blood/ Lymphatic System Disorders	Neutropenia <7 Days without fever	4	No	Yes
Blood/ Lymphatic System Disorders	Thrombocytopenia <7 days without bleeding	4	No	Yes
Blood/ Lymphatic System Disorders	Lymphocyte Count Decrease	4	No	Yes
Blood/ Lymphatic System Disorders	Anemia	4	No	Yes

11.4.4 Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject/patient exposure to the study drug, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF. These events should also be reported to Pharmacyclics within 15 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) and may require enhanced data collection.

Events of special interest to Pharmacyclics include:

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

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakeCT@pcyc.com) or fax ((408) 215-3500) to Pharmacyclics Drug Safety, or designee , within 15 days of the event.

Major Hemorrhage

Major hemorrhage is defined as any of the following:

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

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.6 above.

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

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 90 days after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days (or 90 days for male partners) after the last dose of study drug must be reported. Any occurrence of pregnancy must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old and this must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

Other Malignancies
All new malignant tumors including solid tumors, skin malignancies and hematologic

malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

11.4.5 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

All subjects who receive treatment will be considered evaluable for toxicity. All adverse events (with the exception of disease progression) and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of study drug. Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided. All Grade 3 or Grade 4 adverse events considered related to study drug must be followed until recovery to baseline or Grade ≤1.

Progressive disease should NOT be reported as an adverse event, but instead symptoms/clinical signs of disease progression may be reported. Otherwise, all events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

11.5 Reporting to the Institutional Review Board (IRB)

Investigative sites will report all serious adverse events directly to their IRB per the reporting policy.

11.6 Reporting to the Food and Drug Administration (FDA) and Other Applicable Authorities

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The DF/HCC Overall Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

11.7 Reporting to the NIH Office of Biotechnology Activities (OBA)

N/A

11.8 Reporting to the Institutional Biosafety Committee (IBC)

N/A

11.9 Reporting to Hospital Risk Management

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

11.10 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and the IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

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 Data Submission

Investigative sites are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ. Data should be entered within 14 days of the corresponding visit and within 14 days of the end of a cycle for any forms to be completed per cycle.

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. 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 Principal Investigator and study team.

The DSMC will meet quarterly and/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 for Phase I or II protocols; for gene transfer 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 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by the DF/HCC IRB.
Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.
All decisions of the IRB concerning the conduct of the study must be made in writing.

Per the IST agreement, any amendments to the Protocol or Informed Consent Document must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

N/A

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

This is an open-label, phase II study of ibrutinib in combination with fludarabine, cyclophosphamide, rituximab (iFCR) in previously untreated, younger patients with CLL. Ibrutinib will be given at 420 mg PO daily, the dose that FDA approved for treating CLL patients. Patients will start on cycle 1 day -7 with one week of ibrutinib monotherapy, and FCR will subsequently be introduced on cycle 1 day 1, and administered at standard dosing for up to 6 cycles. Disease assessments will be performed at baseline, after cycle 3, and 2 months after completing combination therapy, and will include CT scan, bone marrow biopsy, and minimal residual disease (MRD) analysis on peripheral blood and bone marrow. At the conclusion of the combination portion, responders will be allowed to continue on ibrutinib maintenance for 2 years, at which point ibrutinib discontinuation may occur as section 14.6. Subjects who need to discontinue FCR early for any reason including cytopenias will be permitted to continue on ibrutinib and will be followed per protocol as long as they do not receive another CLL therapy.

Primary Endpoints:

- Part I: Rate of MRD-negative complete response (CR) in the bone marrow assessed at 2 months after completing the combination therapy.

- Part II: Rate of BM MRD-negativity 2 years after ibrutinib discontinuation in patients who achieve BM MRD-negativity after iFCR induction and 2 years of ibrutinib maintenance

Study Design/Sample Size

Part I: This is a one-stage, single-arm, phase 2 study to determine the MRD-negative CR rate in the bone marrow after treating with iFCR in previously untreated, younger CLL patients. In the previous study with FCR alone without ibrutinib in the same patient population, the MRD-negative CR rate was 20% (Boettcher et al., 2012). We base this as the null hypothesis. With the addition of ibrutinib, we hypothesize that the MRD-negative CR rate will be 40% or higher. Thirty-five patients will be enrolled and if 11 or more patients achieve MRD-negative CR at 2 months post iFCR treatment, we will regard the treatment efficacious. Conversely, if 10 or fewer patients achieve MRD-negative CR, we will regard the treatment inefficacious. With this design, the probability of concluding the treatment efficacious is 0.89 if the true but unknown response rate is 40% and 0.075 if the true rate is 20%. This decision rule is calculated using the exact Clopper-Pearson binomial method (Clopper and Pearson, 1934)**.** Table 1 below shows the operating characteristics of this design. A patient will be considered unevaluable for response and replaced if the patient decides to withdraw from the study prior to the response assessment for the reasons that are unrelated to the treatment.

Table 1. Operating Characteristics

	True but Unknown Response Rate

	20%	25%	30%	35%	40%
Prob(≥11 MRD-negative CR)	0.075	0.24	0.49	0.73	0.89

14.2 Accrual Rate

To accrue 38 patients with MRD-CR, we will accrue a total of 85 patients in this study. Since 35 have already been accrued, an additional 50 patients will be accrued to this new portion of the study. Based on the accrual of Part I of this study and knowing that we no longer have a competing study and are adding 2 new external sites, we anticipate accrual at a rate of about 2.75 patients per month such that the accrual of this study will complete within approximately 18 months from the start of randomization.

14.3 Monitoring Treatment Related Toxicity

Data safety and monitoring will be performed per DFCI guidelines. Although the combination therapy iFCR has been very well tolerated in our pilot data of three patients who received iFCR, we will closely monitor treatment-related toxicity for all participants who receive any amount of iFCR. If in the first 10 patients who receive at least one cycle of iFCR, 3 or more patients develop unexpected toxicity, this will trigger a consultation with the DSMC about whether to stop accrual. Unexpected toxicities would include the following events that occur during the first cycle of treatment, unless they are clearly due to extraneous causes: grade 4 or higher infusion reaction, grade 4 or higher infection, or other grade 3 or higher, clinically significant non-hematologic toxicity related to study treatment, except asymptomatic laboratory abnormalities or nausea/vomiting/diarrhea that improves with supportive care. With this design, the probability of triggering a consultation is 0.07 if the true but unknown rate of grade 3 or higher treatment related toxicity is 10%, 0.18 if the rate is 15%, 0.74 if the rate is 35%, and 0.83 if the rate is 40%.

14.4 Stratification Factors

There will be no stratification of patients on this study.

14.5 Analysis of Secondary Endpoints

The analysis of secondary endpoints will be primarily descriptive, including proportions of the rate of MRD-negative CR in the bone marrow after 3 cycles of iFCR and at 1 year and 2 years after completing the combination portion of the study. Time to MRD-negativity will also be analyzed for patients who achieve MRD-negativity. Associations between the clinical outcome and baseline factors will be tested using Fisher's exact test, chi-square test and Wilcoxon-rank-sum test. The Kaplan Meier (KM) method will be used to summarize progression-free survival and overall survival descriptively. Association between MRD-negative CR and progression-free and overall survival will be tested using Mantel-Byar test (Mantel et al., 1974). Also, if the number of events permits, we will attempt to construct a multivariable proportional hazards model treating MRD-negative CR status as a time dependent variable. Similar univariable and multivariable (if the number of events permits) analysis will be performed for the best MRD negative response, rate of conversion of patients in BM MRD-negative PR to BM MRD-negative

CR, and the kinetics of MRD disappearance and reappearance over time. Association of established CLL prognostic factors (e.g. FISH cytogenetics, *IGHV* status, ZAP70 status) and clinical response, in particular, MRD-negative CR, will be assessed using primarily univariable logistic regression analysis. In addition, appropriate data analysis will be performed for each of laboratory correlative studies.

14.6 Part II: Ibrutinib Discontinuation

Study Design/Sample Size

In the second part (Part II) of the study, we will investigate whether discontinuation of ibrutinib for those patients who achieve bone-marrow (BM) MRD-negativity and receive 2-years of ibrutinib maintenance therapy is feasible without compromising efficacy. For this objective, we will continue to enroll 50 additional patients to the current study to a total of 85 patients. Of these 85, we anticipate that approximately 60 patients (20 from the current cohort of 35 and 40 from the additional 50 patients) will be eligible for Part II. Although the MRD-negative rate is estimated to be 86% in the current cohort of 35 patients, they are allowed to continue treatment and we project that approximately two-thirds of them will decide to discontinue upon completion of the maintenance therapy. Therefore, approximately 20 patients from the current cohort would be eligible for Part II.

The primary endpoint of the Part II study is the 2 year BM MRD-negativity rate. All eligible patients for this second part of the study will receive therapy on the same schedule as patients in Part I, with one week of ibrutinib monotherapy followed by up to 6 cycles of FCR in combination with ibrutinib followed by 2 years of ibrutinib maintenance. During this 2 years of ibrutinib maintenance, patients will be followed with PB MRD testing every 6 months and with a BM MRD assessment at 1 year into maintenance. All patients will undergo a bone marrow biopsy at 2 years into maintenance for MRD assessment. Those patients who have had at least one prior MRD negative results (in either blood or BM) and remain BM MRD negative on this test after 2 years of ibrutinib maintenance will discontinue ibrutinib.

Patients who continue on ibrutinib will follow the same follow-up schedule as in part I. Those who discontinue will be followed for 2 additional years after discontinuation of the maintenance therapy, with PB MRD testing every 3 months and BM MRD testing at 1 year and 2 years post ibrutinib discontinuation. At the end of the follow-up, if the 2-year BM MRD-negativity rate is 85% or higher, we will conclude that discontinuation of the therapy is feasible. If, however, it is 70% or lower, we will conclude that the discontinuation is questionable and will revisit the hypothesis. Table 2 below shows the operating characteristics of this design. For example, if 60 (N) patients are eligible for Part II and if 48 or more patients are alive and BM MRD-negative at 2 years after discontinuation, we will regard discontinuation as feasible. With this design (N=60), the probability of concluding that discontinuation is feasible is 0.89 if the true but unknown 2-year BM MRD-negative rate is 85%, but 0.057 if the rate is 70%. This decision rule is calculated using an exact binomial distribution. A secondary endpoint of the Part II study is the 2 year progression-free (PFS) rate.

Table 2. Operating Characteristics

Sample Size (N)	No. of alive & Progression-free patients (X)	True but unknown PFS rate	
		70%	85%
		Prob (>=X)	
55	44	0.067	0.887
56	45	0.057	0.875
57	46	0.049	0.862
58	46	0.077	0.914
59	47	0.066	0.904
60	48	0.057	0.894
61	49	0.049	0.883
62	50	0.041	0.871
63	50	0.065	0.919
64	51	0.056	0.91
65	52	0.048	0.9

After this 2 year time point, patients will go back to every 6 month peripheral blood MRD testing. If they become MRD positive or if they show other signs of clinical progression of CLL, they will resume ibrutinib monotherapy, which will be continued until time of progression or unacceptable toxicity. Patients will continue to be followed on study for survival analyses but formal response assessments after this time will be at the discretion of the investigator.

Of note, patients in the original cohort of 35 patients recruited to the study who achieve CR with bone marrow MRD-negativity will be given a choice as to whether they will undergo randomization after 2 years of ibrutinib maintenance. Patients recruited to the study in the new cohort who achieve CR with bone marrow MRD-negativity will be required to undergo randomization after 2 years of ibrutinib maintenance.

14.7 Reporting and Exclusions

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

14.7.1 Evaluation of toxicity.

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

Patients who have discontinued ibrutinib due to ibrutinib toxicity are strongly encouraged to remain on study and receive FCR therapy alone as per standard of care.

14.7.2 Evaluation of response.

Only those participants who have received at least one cycle of therapy and have had their disease re-evaluated will be considered evaluable for response. Patients who are inevaluable for response may be replaced.

Each participant will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) death from toxicity, 6) death because of other cause, or 7) unknown (not assessable, insufficient data). By arbitrary convention, category 7 usually designates the "unknown" status of any type of data in a clinical database.

15. PUBLICATION PLAN

The initial results of this study will be made public within 24 months of the end of data collection. Study results will be published in a peer-reviewed journal, but the initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of data collection.

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

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Appendix A: Performance Status Criteria

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

Appendix B: Inhibitors and Inducers of CYP3A

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

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors: INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE NEFAZODONE SAQUINAVIR TELITHROMYCIN **Moderate inhibitors:** Aprepitant Erythromycin diltiazem Fluconazole grapefruit juice Seville orange juice Verapamil **Weak inhibitors:** Cimetidine **All other inhibitors:** Amiodarone NOT azithromycin Chloramphenicol Boceprevir Delavirdine diethyl-dithiocarbamate Fluvoxamine Gestodene Imatinib Mibefradil Mifepristone Norfloxacin Norfluoxetine star fruit Telaprevir Troleandomycin	Carbamazepine Efavirenz Nevirapine Barbiturates Carbamazepine Glucocorticoids Modafinil Oxcarbazepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's Wort Troglitazone

Appendix C: Cairo-Bishop Tumor Lysis Syndrome Criteria and Child-Pugh Scoring

Cairo-Bishop Definition of Tumor Lysis Syndrome (Cairo MS et al., 2004)

Laboratory Tumor Lysis Syndrome (LTLS):

Uric Acid ≥ 476 µmol/l (≥ 8.0 mg/dl) or 25% increase from baseline
Potassium ≥ 6.0 mmol/l (≥ 6.0 mEq/l) or 25% increase from baseline
Phosphorous ≥1.45 mmol/l (≥ 4.5 mg/dl) or 25 % increase from baseline
Calcium ≤ 1.75 mmol/l (≤ 7.0 mg/dl) or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).

Clinical Tumor Lysis Syndrome (CTLS):

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted)
2. Cardiac arrhythmia / sudden death
3. Seizure*

ULN, Upper limit of normal
*Not directly attributable to a therapeutic agent

Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	**-**	0 - ≤ 1.5 x ULN	*None*	*None*
1	+	1.5 x ULN	Intervention not indicated	*None*
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device.	Seizure in which consciousness is altered; poorly controlled seizure disorder; break through generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control

5	+	Death*	Death*	Death*

ULN, upper limit of normal; ADL, activities of daily living

*Probably or definitely attributable to clinical TLS

Child-Pugh Score

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

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

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Appendix D NCI CTC Version 4.03

Toxicity will be scored using NCI CTC Version 4.03 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.03 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC Version.

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APPENDIX E: Dana -Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

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 should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

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. Within DF/HCC, this person is the Overall Principal Investigator 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. 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, **Mathew 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 reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- 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.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC ODQ.
- 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.
- 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 local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local 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.

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 to interventional trials (i.e. drug and/or device trials).

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, 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 DF/HCC ODQ 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

See **Sections 4.3 and 4.4** of the protocol.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment 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 deviation 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 treatment 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 **Section 11** of the protocol.

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 and 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 **Section 7** of the protocol. .

Participating Institutions should order their own agent regardless of the supplier

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 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 ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

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.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is 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, 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 Notification

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 these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. 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 and 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.