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Title: A Phase I/II Study of IPI-145 in Combination with Fludarabine, Cyclophosphamide, and Rituximab (iFCR) in Previously Untreated, Younger Patients with Chronic Lymphocytic Leukemia

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Agent(s):
IPI-145 – Verastem, Needham, MA
Fludarabine (commercial)
Cyclophosphamide (commercial)
Rituximab (commercial)

SYNOPSIS

Study Title: A Phase I/II Study of IPI-145 in Combination with Fludarabine, Cyclophosphamide, and Rituximab (iFCR) in Previously Untreated, Younger Patients with Chronic Lymphocytic Leukemia

Study Overview: An open-label, phase I/II study of IPI-145 in combination with fludarabine, cyclophosphamide, rituximab (iFCR) will be performed. The phase I part is a standard 3+3 design with three dose levels. Patients will start on day -7 with one week of IPI-145 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. FCR will subsequently be introduced on day 1, and administered at standard dosing for 6 cycles, with dose reductions permitted. Patients achieving either a PR or CR will be allowed to continue on IPI-145 maintenance for up to 2 years after completing chemotherapy. Conversion to MRD negativity and 2 year progression-free survival will be assessed for these patients.

Primary Objectives

- To assess the safety of IPI-145 in combination with FCR in previously untreated younger patients with CLL
- To determine the rate of minimal residual disease negative complete response (MRD negative CR) in the bone marrow at 2 months post last cycle of FCR

Secondary Objectives

- To determine clinical response, including overall response rate, complete and partial response rates, progression-free survival, overall survival, and duration of remission as determined by 2008 IW-CLL criteria
- To assess rate of minimal residual disease (MRD) in the peripheral blood
- To determine rates of treatment-related adverse effects
- To determine the association of established CLL prognostic factors (e.g. FISH cytogenetics, *IGHV* status, ZAP70 status) with clinical response

Exploratory Objectives:

- To assess for an association of novel prognostic factors such as BH3 profiling with clinical response
- To assess the change in pharmacodynamic markers such as p-AKT, p-ERK, and Ki-67
- To evaluate genomic analyses for association of response with mutation status of *SF3B1, TP53, NOTCH1, MYD88* and the *BCR/NFKB* pathway

Schedule of Administration

IPI-145 will be administered orally daily or twice daily during each 28-day cycle. FCR will be given at standard dosing, with dose reductions permitted as per usual standards of care. Patients will be evaluated for DLTs throughout the course of the study. At the conclusion of 6 cycles of iFCR therapy, patients with a partial or complete response will be able to continue on to a maintenance phase of IPI-145 monotherapy for up to 2 years in the absence of progressive disease.

Dose Escalation

Three doses of IPI-145 will be considered to determine MTD of IPI-145 in combination of FCR: 15 mg QD (dose level -1), 25 mg QD (dose level 1, starting dose), 25 mg bid (dose level 2). Dose limiting toxicities (DLTs) and the observation period are defined below and in section 5.3.

A cohort of 3 patients will enter at a dose level, starting dose level 1. If no DLT is seen in the first 3 patients, then a dose escalation will take place. If 2 or more of the first 3 patients experience DLT at dose level 1 or 2, then the next cohort of 3 patients will be treated at the next lower dose level, unless 6 patients have already been treated at that dose level. If 2 or more of the first 3 patients experience DLT at dose level -1, then the study will be terminated early. If 1 of the 3 patients at a dose level experiences a DLT, then 3 additional patients will be treated at that dose level. If there is no DLT in the 3 additional patients then dose escalation will take place. If this is dose level 2 or -1, then this dose level will be the MTD. If 1 or more of the 3 additional patients experience(s) DLT then the MTD is considered to have been exceeded, and 3 more patients will be treated at the next lower dose, unless 6 patients have already been treated at that dose level. If this is does level -1, then the study will be terminated early. A minimum of six patients must be entered at the MTD, and fewer than 2 patients in 6 should experience DLT. If 0 in 6 patients experience DLT at dose level 2, this dose level will be the RP2D (recommended Phase II dose).

Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting toxicities (DLTs) occurring during the first cycle of treatment will be used in determining the recommended phase II dose (R2PD). DLTs that occur at any time on treatment will be evaluated with regard to the stopping rules as detailed in the protocol.

A DLT will be defined as:

- Any Grade 3 or greater hematologic toxicity with exceptions for Grade 3 or Grade 4 neutropenia or thrombocytopenia that persists for ≤ 10 days off treatment.
- Any Grade 3 or greater non-hematologic toxicity with the following exceptions:
    - Grade 3 or greater nausea/vomiting/diarrhea despite optimal supportive care that persists for 7 days or less
    - Grade 3 infusion reactions
    - Grade 3 asymptomatic laboratory abnormalities that improve to grade 2 or less within 3 days
- Inability to receive day 1 therapy of Cycle 2 even after a three week treatment delay due to continued drug related toxicity from the prior cycle.
- All toxicities will be considered relevant to determining DLT and to reporting unless the event can clearly be determined to be unrelated to the study drug(s).
- Any Grade 4 or greater elevation in ALT/AST.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 will be used to grade toxicities during the trial unless otherwise specified.

Study Drug
IPI-145 is administered orally as a capsule formulation. The IPI-145 drug product is supplied as 5 mg and 25 mg formulated capsules.

Inclusion Criteria

- Must have a confirmed diagnosis of CLL and an indication for treatment as per IW-CLL 2008 criteria
- No prior therapy for CLL due to the patient's meeting IW-CLL 2008 criteria for treatment
- Age greater than or equal to 18 years and less than or equal to 65
- Life expectancy of greater than 6 months
- ECOG performance status $\leq$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

- Patients receiving any other study agents
- Patients with known CNS involvement
- Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations limiting compliance with study requirements
- Pregnant women are excluded from this study because IPI-145 is an agent with the potential for teratogenic or abortifacient effects
- Individuals with a history of a different malignancy are ineligible except for the following circumstances: disease-free for at least 2 years and deemed by the Principal Investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated with curative intent within the past 5 years: cervical cancer in situ, localized prostate cancer, and skin cancer including basal cell, squamous cell carcinoma, or melanoma *in situ*
- HIV-positive individuals
- Inadequate hepatic function defined by aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >2.5 x upper limit of normal (ULN); direct bilirubin >1.5 x ULN unless due to hemolysis or Gilbert's syndrome.
- Inadequate renal function defined by serum creatinine >1.5 x ULN
- Baseline QTcF >480 ms. NOTE: This criterion does not apply to patients with a left bundle branch block.
- Concurrent treatment with any agent known to prolong the QTc interval (see Appendix E).
- Patients with a history of active tuberculosis within the preceding two years
- Patients who have had a venous thromboembolic event (e.g., PE or DVT) requiring anticoagulation and who meet any of the following criteria:
    - Have been on a stable dose of anticoagulation for <1 month
    - Have had a Grade 2, 3 or 4 hemorrhage in the last 30 days

- Are experiencing continued symptoms from their venous thromboembolic event (e.g. continued dyspnea or oxygen requirement)

NOTE: Patients who have had a venous thromboembolic event but do not meet any of the above three criteria are eligible for participation.

- Patients with a history of alcohol abuse, chronic hepatitis, or other chronic liver disease (other than direct CLL liver involvement).
- NOTE: Chronic hepatitis includes active infection with hepatitis B or C. All patients will be tested for hepatitis C virus antibodies (HCV Ab) and hepatitis B surface antigen (HBsAg) at screening. Patients with a positive result for HBsAg or HCV Ab will be excluded from enrolling in this study.
- Concurrent administration of medications or foods that are strong inhibitors or inducers of CYP3A (see Appendix C).
- Presence of active infection within 72 hours of treatment. 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

Statistical Methodology

Phase I
A standard 3 + 3 dose escalation design with 3 dose levels is used in the phase I portion for assessing safety and determining the recommended dose for the phase II portion of this study of IPI-145 in combination of FCR in previously untreated CLL patients. IPI-145 will be the only escalating drug, with FCR given at standard dosing.

Phase II
After RP2D is established in phase I, 20 additional patients will be enrolled in the phase II study and treated with IPI-145 at the RP2D + FCR so that a total of 26 patients will be treated at the RP2D. The primary objective for the phase II portion of the study is to determine the rate of minimal residual disease negative complete response (MRD-negative CR) in the bone marrow at the re-staging evaluation 2 months after completing FCR chemotherapy.

Study Design

Phase I

A standard 3+3 design with three doses of IPI-145.

Phase II

A single stage study which consists of determining the MRD-negative CR rate in the bone marrow at 2 months post IPI-145 + FCR in previously untreated CLL patients. An exact one sample binomial test is used to compute the sample size. Twenty additional patients will be enrolled and analyzed in conjunction with the 6 patients from the phase I portion treated at the

MTD/RP2D for a total of 26 patients. Twenty-six patients are needed in order to detect a 45% MRD-negative CR rate, assuming the MRD-negative CR rate for the null hypothesis is 20% (Boettcher et al., 2012) and 90% power and 6% one-sided type I error. The null hypothesis will be rejected if 9 or more MRD-negative CRs are observed.

Analysis of Secondary Endpoints

Clinical response, including overall response rate, complete and partial response rates determined by IW-CLL criteria as well as rate of MRD negativity in the peripheral blood will be summarized as percentages and 90% CI will be calculated using exact binomial test. The Kaplan Meier method will be used to summarize progression-free survival and overall survival descriptively. Association of established CLL prognostic factors (e.g. FISH cytogenetics, *IGHV* status, ZAP70 status) and clinical response will be assessed using Fisher's exact test for categorical variables and Wilcoxon's rank sum test for continuous variables. In addition, a correlation analysis between peripheral blood and bone marrow MRD negativity will be performed. Toxicity will be reported descriptively. Association between clinical outcome and exploratory endpoints will be evaluated. Exploratory endpoints include BH3 profiling, change in pharmacodynamic markers such as p-AKT, p-ERK, and Ki-67, and genomic analysis with mutation status of *SF3B1, TP53, NOTCH1, MYD88* and the *BCR/NFKB* pathway.

Sample Size/Accrual Rate

Planned Sample Size: Minimum: 4, Maximum: 32
Estimated Monthly Accrual: 2-3
Follow-up: Patients completing 2 years of maintenance IPI-145 or those who do not go on to receive IPI-145 maintenance will be followed until initiation of new therapy, or death.

SCHEMA

Phase I

If DLT in	Then	If DLT in	Then
0/3 →	Escalate to the next dose level	-	-
1/3 →	Add 3	1/6 →	Escalate to next dose level (or accrue 20 additional if this is the MTD)
		≥ 2/6 →	De-escalate to previous dose level
≥ 2/3 →	MTD is the prior dose level		

Dose-Escalation Schedule 1 cycle = 28 days (except cycle 1 [28 days plus 7 day lead in])		
	Dose Level	**Dose of IPI-145**
	2	**25 mg BID**
Starting Dose →	**1**	**25 mg QD**
	-1	**15 mg QD**

Phase II

Definitions

CR - Complete Response

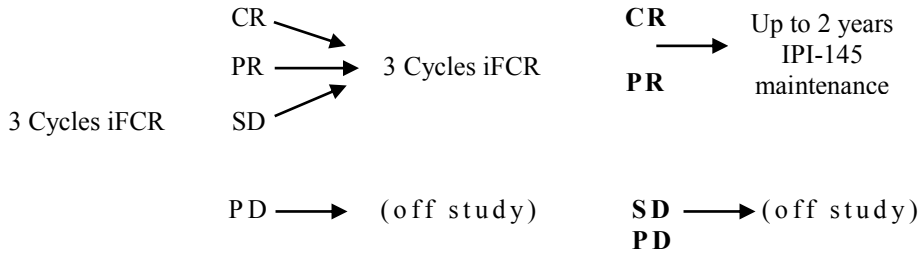
PR - Partial Response

PD - Progressive Disease

SD - Stable Disease

FCR – Fludarabine, Cyclophosphamide, Rituximab

i – IPI-145



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1. OBJECTIVES

1.1 Study Design

An open-label, phase Ib/II study of IPI-145 in combination with fludarabine, cyclophosphamide, rituximab (iFCR) will be performed in previously untreated CLL patients age 65 or younger with good performance status. The phase I part is a standard 3+3 design with three dose levels. Patients will start on day -7 with one week of IPI-145 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. FCR will subsequently be introduced on day 1, and administered at standard dosing for 6 cycles, with dose reductions permitted (see Section 6.2). Patients achieving either a PR or CR will be allowed to continue on IPI-145 maintenance for up to 2 years after completing chemotherapy. Conversion to MRD negativity and 2 year progression-free survival will be assessed for these patients.

1.2 Primary Objectives

- To assess the safety of IPI-145 in combination with FCR in previously untreated younger patients with CLL
- To determine the rate of minimal residual disease negative complete response (MRD-negative CR) in the bone marrow at 2 months post last cycle of FCR

1.3 Secondary Objectives

- To determine clinical response, including overall response rate, complete and partial response rates, progression-free survival, event-free survival, and duration of remission as determined by 2008 IW-CLL criteria
- To assess rate of minimal residual disease (MRD) in the peripheral blood
- To determine rates of treatment-related adverse effects
- To determine the association of established CLL prognostic factors (e.g. FISH cytogenetics, *IGHV* status, ZAP70 status) with clinical response

1.4 Exploratory Objectives

- To evaluate the association of novel prognostic factors such as BH3 profiling and somatic mutations in *SF3B1, NOTCH1, MYD88* and the *BCR/NFKB* with clinical response
- To measure the change in pharmacodynamic markers such as p-AKT, p-ERK, and Ki-67 during initial therapy

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 was 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 to 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.

Limitations of Current Therapy
Because of these encouraging results, FCR has become the standard of care for previously untreated fit 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.

Moreover, FCR has significant limitations. For example, patients with high risk markers such as del(17p) have markedly inferior outcomes, with poor CR rate (5%) and 3-year progression-free (18%) and overall survival (38%). Furthermore, patients in all risk groups receiving FCR inevitably relapse, with a median progression free survival (PFS) of about 4.5 years. 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 Inhibition
Recently, it was recognized that the B cell receptor (BCR) pathway is a promising, novel target for the treatment of CLL. Although not activated by somatic mutation, nonetheless the BCR pathway is constitutively active in CLL and further inducibly activated within microenvironmental niches. Increasing evidence suggests that phosphatidylinositol 3-kinase (PI3K) inhibitors can have a profound impact on modulating the CLL microenvironment. For example, the delta-isoform specific PI3K inhibitor idelalisib (GS1101) was found *in vitro* to inhibit microenvironmental protection by releasing CLL cells from stroma, thereby leading to increased CLL cell susceptibility to cell death (Hoellenriegel et al, 2011). These promising preclinical results of PI3K inhibition in CLL have translated into the clinic, where a phase I trial of idelalisib showed that 84% of CLL

patients achieved a lymph node response (Furman et al., 2010). Interestingly, the majority of patients had a greater than 50% increase in lymphocyte count from baseline, providing strong evidence of the ability of PI3K inhibition to cause decreased CLL cell adhesion from stroma *in vivo,* a phenomenon that has been named 'lymphocyte redistribution'.

Though promising, PI3K-δ specific inhibition has potential limitations. For example, by targeting only the δ-isoform of PI3K, CLL cells could theoretically develop resistance through upregulation of other PI3K isoforms. Furthermore, there is increasing interest in the protective role that the PI3K-γ isoform plays in T cells and other immune cells in the CLL microenvironment (Ciraolo, et al., 2011). Therefore, exploring the use of a PI3K inhibitor with activity against both the δ and γ isoforms is appealing.

IPI-145

IPI-145 is a potent oral inhibitor of both PI3K-δ (K_d: 23 pM) and PI3K-γ (K_d: 243 pM). The drug has been well-tolerated in patients with relapsed or refractory CLL at doses up to 75 mg bid, with the most common related AEs being respiratory and infectious events as well as cytopenias and ALT/AST elevations, neither of which were dose-related, and both of which were manageable by dose interruption or dose reduction. As of 28 October 2013, 47 subjects with relapsed/refractory CLL/SLL had available efficacy data (Flinn et al., 2013). Their median time on treatment was 5.5 months (range: 0.9 to 22.8 months). Subjects dosed at ≤25 mg BID (n=27) had been on study longer (median=7.6 months) compared to subjects dosed at 75 mg BID (n=20, median=3.6 months). The investigator-reported ORR [(CR + PR), as defined by the IWCLL/IWG] was 47% among the 47 subjects with a response assessment, which included 1 CR, and 21 PR.

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/m^2 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 (Hainsworth et al, 2003, 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 **IPI-145**

INTRODUCTION

IPI-145 is a potent phosphoinositide-3-kinase (PI3K)-δ,γ inhibitor being developed by Infinity Pharmaceuticals, Inc. (Infinity) based in Cambridge, MA. The PI3K-δ and PI3K-γ isoforms are necessary for adaptive and innate immunity, and are important mediators in inflammatory disorders and hematologic malignancies. Therefore, IPI-145 is being developed as an orally administered potential therapeutic in hematologic malignancy and inflammatory disease indications.

BACKGROUND

Functions of PI3K-δ and PI3K-γ

There are four mammalian isoforms of class 1 PI3Ks: PI3K-α, β, δ (class 1a PI3Ks) and PI3K-γ (a class 1b PI3K) (reviewed in Davids et al., 2013). These PI3Ks catalyze the production of phosphatidylinositol (3,4,5)-trisphosphate (PIP3), leading to activation of the downstream effector pathways important for cellular survival, differentiation, and function. PI3K-δ and P13K-γ are preferentially expressed in leukocytes, and are important in leukocyte function.

PI3K-δ is activated by cellular receptors (e.g., receptor tyrosine kinases) through interaction with the SH2 domains of the PI3K regulatory subunit (p85), or through direct interaction with RAS. PI3K-γ is associated with G-protein coupled receptors (GPCRs), is responsible for the very rapid induction of PIP3 in response to GPCRs, and can be also activated by RAS downstream of other receptors. PIP3 produced by PI3K activates effector pathways downstream through interaction with pleckstrin homology (PH) domain containing enzymes (e.g., PDK-1 and AKT [PKB]). It is clear that both PI3K-δ and PI3K-γ isoforms are also important for chemotaxis and cell migration.

PI3K in Immune Cells

PI3K-δ is important in B-cell function including development, activation, chemotaxis, migration, and homing to lymphoid tissue, and inhibitors of PI3K-δ block these functions. In T-cells, PI3K-γ has demonstrated a role in receptor and cytokine signaling. PI3K-γ is important for T-cell function including proliferation, activation, and differentiation (Subramaniam et al., 2012). PI3K-δ along with PI3K-γ, are important in the response to immune complexes and FCγRII signaling in neutrophils, including migration, and the neutrophil respiratory burst. PI3K-γ is also critical for the migration and function of neutrophils, suggesting a role in tumor immunity and cancer progression (Randis et al., 2008). As such, PI3K-δ and PI3K-γ are important mediators of cancer pathogenesis.

Non-Clinical Summary of IPI-145

Pharmacology of IPI-145

In vitro enzymatic assays indicate that IPI-145 is a potent PI3K-δ,γ inhibitor and inhibits proliferation of stimulated human B and T lymphocytes in cell-based assays. Cellular analysis demonstrates IPI-145 inhibits the phosphorylation of downstream markers of PI3K activation, such as AKT and ribosomal S6, in a concentration-dependent manner.

Summary of Absorption, Distribution, Metabolism, and Excretion (ADME) of IPI-145

The single-dose pharmacokinetics of IPI-145 following oral (PO) and intravenous (IV) administration have been characterized in mouse, rats, dogs and monkeys.

In general, the ADME studies demonstrated that IPI-145 was rapidly and extensively absorbed across the nonclinical species with bioavailability values ranging from 40 to 97%, with the exception of the mouse where the bioavailability was lower (7%). The half-life of IPI-145 was 5 hours in monkeys, and less than or equal to 2 hours in the other nonclinical species. IPI-145 is a P-gp substrate with the potential to inhibit the active transport of other P-gp substrates. Plasma protein binding of IPI-145 was high in human and across several nonclinical species, with the free fraction being concentration- and species-dependent. The oxidative metabolism of IPI-145 was primarily through CYP3A4 with potential minor involvement by CYP1A2, CYP2C8, and CYP2B6. In vitro, IPI-145 is an inhibitor of CYP3A4 and CYP2C8, and a weak inducer of CYP2B6 at high concentrations only.

Summary of IPI-145 Toxicology

IPI-145 has been assessed in a series of nonclinical studies which included safety pharmacology, genetic toxicology, and general toxicology studies with durations of treatment ranging from single-dose administration in monkeys to 4 weeks of repeat-dose administration in rats and monkeys. The nonclinical safety assessment program was designed to support oral administration in healthy subjects as well as oncology patients. The rat and monkey were selected for nonclinical safety assessment based on achievable exposure levels following oral administration, and the similarity of the *in vitro* metabolic profiles when compared to the human *in vitro* metabolic profile. Additionally, the monkey was chosen because of the similarity of its immune system to that of humans.

IPI-145 treatment-related findings fell into two general types. The first type consisted of on-target effects of IPI-145, including depletion of lympho-hematopoietic cells in lymphoid and hematopoietic tissues. The second type consisted of inflammatory, degenerative and regenerative changes in various tissues. In monkeys, these changes were due to opportunistic infections (primarily viral, but also protozoal, fungal, and bacterial). It is likely that these findings were due to immune suppression as a secondary response to the first type of effects.

The no observed adverse effect level (NOAEL) in rats was the low-dose of 5 mg/kg/day in the Good Laboratory Practice (GLP) 4-week repeat-dose toxicity study based on adverse changes in the lymphoid and hematopoietic systems, adrenal, gastrointestinal (GI) tract, testis, and uterine observed at ≥ 50 mg/kg/day. At the NOAEL, non-adverse, an on-target effect of increase in the cellularity of white pulp periarteriolar sheath accompanied by decrease in marginal zone cellularity

was observed in the spleen. The severely toxic dose to 10% of animals (STD10) in rats was the mid-dose of 50 mg/kg/day in the GLP 4-week repeat-dose toxicity study based on mortality at 350 mg/kg/day.

In cynomolgus monkeys, once daily oral administration of IPI-145 for 28 days elicited dose-dependent, on-target immunosuppressive effects, characterized by lymphoid depletion and bone marrow changes. In monkeys, the highest non-severely toxic dose (HNSTD) was 5 mg/kg/day in the GLP 4-week study based on adverse clinical signs and/or moribundity observed at ≥ 30 mg/kg/day.

Clinical Studies in Humans

Study IPI-145-01 (Phase 1, first-in-human study)

Study IPI-145-01 was a randomized, double-blind, placebo-controlled, Phase 1 study in healthy adult subjects designed to evaluate the safety, tolerability, PK and pharmacodynamics of single and multiple ascending doses of IPI-145 and to assess the effect of food and ketoconazole on the PK of IPI-145. One-hundred and six (106) subjects were enrolled. In this setting IPI-145 was well tolerated at the doses evaluated. There were no deaths and no serious adverse events (SAEs).

Pharmacokinetic assessments demonstrated that IPI-145 is rapidly absorbed following single and multiple oral dose administration, with the maximum plasma concentration observed typically 1 hour after dosing. Across the dose ranges evaluated, IPI-145 exposure increased proportionally to dose. The mean elimination half-life ranged from 6.5 to 11.7 hours after repeat dosing and did not depend on the dose level administered. IPI-145 accumulation was less than 2-fold following 14 days of Q12 h oral administration.

Data from the drug-drug interaction (DDI) portion indicated that concomitant administration of 200 mg ketoconazole every 12 hours (Q12 hr) increased exposure to IPI-145. On average, $C_{max,}$ $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ increased by approximately 66%, 285% and 295%, respectively, in the presence of ketoconazole compared to IPI-145 administered alone.

Study IPI-145-02 (Phase 1, Hematologic Malignancies)

Study IPI-145-02 is a Phase 1, open-label, dose-escalation study of IPI-145 administered orally twice daily during each 28-day cycles at doses ranging from 8 mg BID to 100 mg BID in adult subjects with advanced hematologic malignancies. The dose-escalation phase of the trial is complete and the expansion phase is ongoing. As of 28 October 2013, a total of 193 subjects, including 67 patients diagnosed with CLL/SLL (15 patients were treatment naïve and 52 patients were relapsed/refractory), have been dosed in the study. The maximum tolerated dose (MTD) was determined to be 75 mg BID based upon two dose limiting toxicities (DLTs) experienced by two subjects receiving 100 mg BID (Grade 3 rash and Grade 3 alanine aminotransferase [ALT]/aspartate aminotransferase [AST] elevations).

Clinical Safety

As of 28 October 2013, 193 patients have received at least one dose of IPI-145 at doses ranging from 8 mg BID to 100 mg BID. Overall, 61 patients have received the proposed dose of 25 mg BID in 28-day cycles. Of the 52 relapsed/refractory CLL/SLL patients enrolled, 25 patients have received a dose of 25 mg BID of IPI-145.

The clinical safety data as of 28 October 2013 collected for patients on 25 mg BID in the overall population (n=61) and in the relapsed/refractory CLL/SLL population (n=25 patients who received 25 mg BID), suggest this dose is well tolerated with a safety profile similar to what might be expected in patients with advanced hematologic malignancies.

Frequently occurring (≥ 20% patients) adverse events observed in relapsed/refractory CLL/SLL patients receiving 25 mg BID included neutropenia (40%), diarrhea (32%), rash (combined terms) (32%), fatigue (28%), anemia (24%), ALT or AST increased (24%), cough (24%), pyrexia (24%), hyperglycemia (20%), nausea (20%) and sinus congestion (20%). Serious adverse events occurring in more than 1 relapsed/refractory CLL/SLL patient at 25 mg BID included febrile neutropenia (3 [12%]), disease progression (2 [8%]), and stomatitis (2 [8%]). Other notable serious events were infections, including upper respiratory infections and pneumonias.

These events are not unexpected based on the patient population and the mechanism of action of IPI-145. Infection prophylaxis and dose modifications included in this protocol are intended to reduce the risk of the frequently occurring events.

Clinical Efficacy

As of 28 October 2013, 47 subjects with relapsed/refractory CLL/SLL had available efficacy data. Their median time on treatment was 5.5 months (range: 0.9 to 22.8 months). Subjects dosed at ≤25 mg BID (n=27) had been on study longer (median=7.6 months) compared to subjects dosed at 75 mg BID (n=20, median=3.6 months).

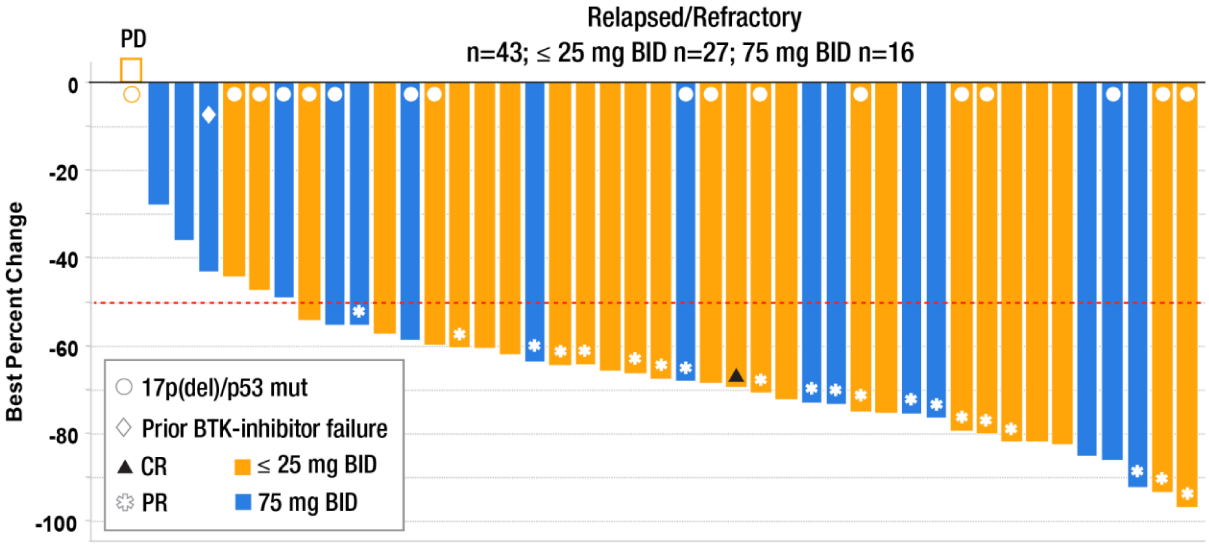
The investigator-reported ORR [(CR + PR), as defined by the IWCLL/IWG] was 47% among the 47 subjects with a response assessment, which included 1 CR, and 21 PR. Table 1 below shows the response rate by IWCLL/IWG in CLL/SLL subjects.

Table 1: Clinical Responses in Subjects with Relapsed/Refractory CLL/SLL (as of 28 October 2013) from Study IPI-145-02

Population	Patients (n)	Best Response (n)				ORR by IWCLL (CR + PR)
	Evaluable	CR	PR	SD	PD	
Overall R/R CLL	47	1	21	24	1	47%
≤ 25 mg BID	27	1	12	13	1	48%
75 mg BID	20	0	9	11	0	45%

The overall response rate in subjects with CLL/SLL was similar between dose cohorts (48% for the 27 subjects who received ≤25 mg and 45% for the 20 subjects who received 75 mg BID and had a response assessment). The median time to response was 1.9 months (range: 1.7 to 8.25), with no variation between dose groups (median 1.9 months for 25 mg BID and 75 mg BID). Figure 1 shows the proportion of patients with a nodal response in CLL/SLL treatment with IPI-145 in Study IPI-145-02.

Figure 1: Maximum Change in Adenopathy by CT Scan Assessment in Subjects with Relapsed/Refractory CLL (as of 28 October 2013) from Study IPI-145-02



Pharmacokinetics

Preliminary PK data from Study IPI-145-02 demonstrate IPI-145 is rapidly absorbed following oral dosing in subjects with advanced hematologic malignancies, with the maximum plasma concentration (C_{max}) generally achieved at approximately 1 hour post-dose. Steady state exposure over the dosing interval (AUC_{0-12}) is proportional to dose. Following repeat dose

administration of 25 mg BID, mean C_{max} and AUC_{0-12} values are 1460 ng/mL and 8129 ng*h/mL, respectively. IPI-145 elimination half-life ($t_{1/2}$) does not appear to vary with dose and the mean $t_{1/2}$ was 4.5 hours following 25 mg BID administration.

RATIONALE FOR IPI-145 AS A POTENTIAL THERAPY FOR PATIENTS WITH CLL

In CLL, activation of the B cell receptor (BCR) pathway leads to upregulation of PI3K-δ, suggesting that PI3K-δ inhibition could have therapeutic benefit in these cancers. We previously showed that primary CLL cells are inhibited from undergoing apoptosis through BCR stimulation by stromal cells or anti-IgM stimulation. The PI3K-δ isoform specific inhibitor idelalisib (also known as CAL-101 or GS-1101) was able to de-adhere CLL cells from stroma and increase their susceptibility to apoptosis induced by other agents (Davids et al., 2012).

Idelalisib has demonstrated promising clinical activity in patients with hematologic malignancies. In heavily pre-treated patients with refractory CLL and bulky lymphadenopathy, single agent idelalisib was highly active and clinically efficacious, providing a durable clinical benefit (Brown et al., 2014). Moreover, inhibition of PI3K-δ not only affected cancer cells directly, but it also affected the ability of the cancer cells to interact with their microenvironment. In refractory or relapsed CLL patients, idelalisib has been combined with bendamustine and rituximab, and this combination of PI3K inhibitor and chemotherapy was well-tolerated with robust clinical activity (Barrientos et al., 2013).

IPI-145 is a potent PI3K-δ inhibitor and would be expected to have at least comparable activity in CLL in combination with chemotherapy. In addition, the ability of IPI-145 to inhibit the gamma isoform of PI3K suggests that the drug may be even more potent than delta-specific inhibitors.

DETERMINATION OF IPI-145 STARTING DOSE AND REGIMEN

Dose levels of IPI-145 ranging from 8 mg BID to 100 mg BID were evaluated in Study IPI-145-02, a Phase 1, open-label, dose-escalation study in subjects with advanced hematologic malignancies where IPI-145 was administered orally twice daily (BID) continuously in 28-day cycles as a single agent. The dose-escalation phase of Study IPI-145-02 is complete and the maximum tolerated dose was determined to be 75 mg BID. Enrollment is complete and a total of 193 subjects have been dosed in the study as of 28 October 2013.

Based on the available data, the following findings were considered in determining the dose and schedule for this study:

- Of the 27 relapsed/refractory CLL/SLL patients with evaluable efficacy data who received ≤ 25 mg BID of IPI-145, the best response to date shows 1 patient achieved a CR and 12 patients have achieved a PR based on IWCLL 2008 response criteria;
- The median time to response (n=12) was rapid (1.9 months) with a PR observed in 6 patients after 2 cycles, in 4 patients after 4 cycles, and in 2 patients after 6 cycles of IPI-145 treatment;
- 85% (11/13) of the relapsed/refractory CLL/SLL patients with evaluable efficacy data who received ≤ 25 mg BID of IPI-145 with stable disease have demonstrated a nodal response, defined as >50% reduction in adenopathy based on CT scans. Eight of 11 patients experienced a nodal response after 2 cycles of IPI-145 treatment; and

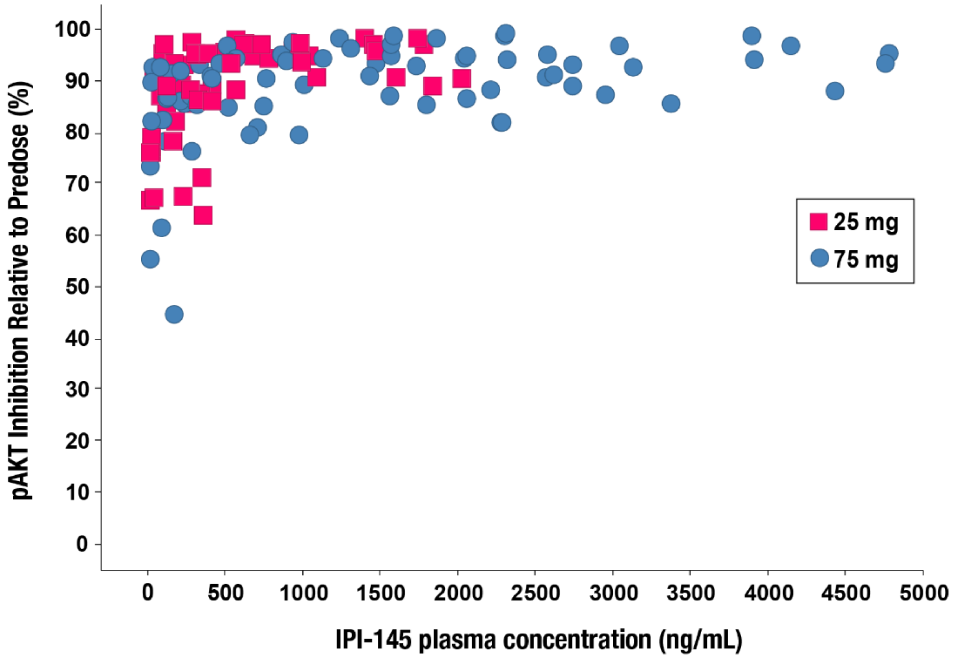
- After 2 cycles of IPI-145 treatment, a nodal response was reported in 4 out of the 6 patients who went on to achieve a PR after 4-6 cycles of IPI-145 treatment. These data introduce the possibility that nodal responses (>50% reduction in adenopathy) may be a precursor of response as defined by the IWCLL criteria. In clinical studies of other therapies in development in CLL, it has been reported that nodal responses have preceded PRs or CRs. [20]

Pharmacodynamics

Preliminary exposure-response analyses observed in Study IPI-145-02 support the rationale that IPI-145 dosed at 25 mg BID or less is expected to be efficacious. Increased exposure did not result in greater reductions in adenopathy.

The serine/threonine kinase AKT is directly phosphorylated by PI3Ks, therefore the reduction in phosphorylated AKT (pAKT) was used as a pharmacodynamic marker for tumor cell PI3K inhibition in subjects with CLL in Study IPI-145-02. Percent pAKT inhibition versus IPI-145 plasma concentration following a single dose is depicted in Figure 2. IPI-145 inhibits phosphorylation of AKT in a concentration-dependent manner, with maximal effects observed at concentrations observed following a 25 mg dose of IPI-145. Further elevations in IPI-145 plasma concentration did not provide additional inhibition of pAKT.

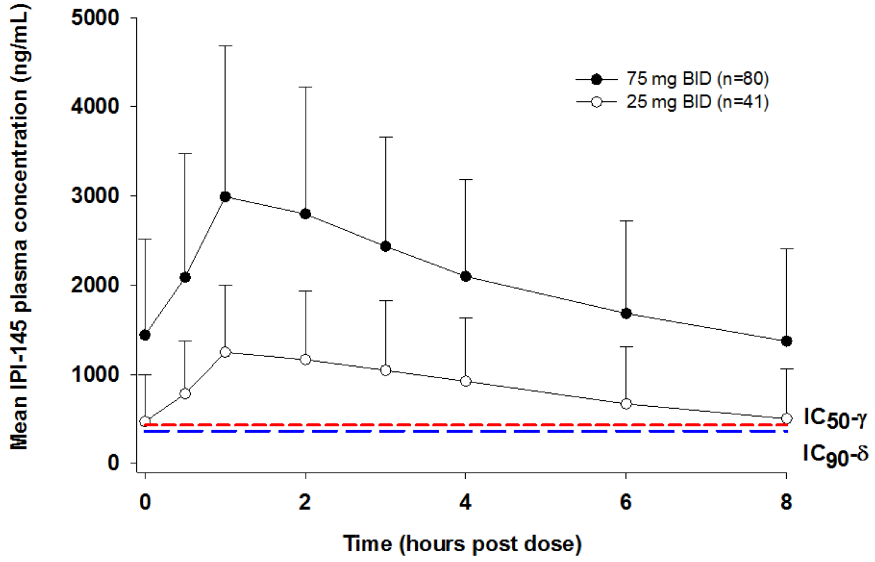
Figure 2: IPI-145 Plasma Concentration Versus Tumor Cell pAKT Inhibition Following a Single Dose in CLL/SLL Patients (Study IPI-145-02; preliminary)



The potential of IPI-145 to inhibit PI3K-δ and PI3K-γ was evaluated *in vitro* through quantitation of the reduction in CD63 cell surface expression on CCR3+ basophils in donor whole blood following stimulation with FcεR1 (PI3K-δ dependent) and fMLP (PI3K-γ dependent). Mean plasma concentrations following 25 mg BID remained at or above the IC_{90} for

PI3K-δ inhibition and near or above the IC_{50} for PI3K-γ inhibition throughout the dosing interval (Figure 3).

Figure 3: Mean IPI-145 Plasma Concentration-Time Profiles on Cycle 2, Day 1 (Study IPI-145-02; preliminary data)



Based on the data above, a dose of 25 mg bid is being pursued in future studies of IPI-145 monotherapy. However, since IPI-145 has not previously been combined with FCR chemoimmunotherapy, we plan to initiate dosing in this study conservatively with IPI-145 at 25 mg QD, a dose that is also anticipated to have efficacy but is less likely to cause unanticipated toxicity than the full dose of 25 mg bid. If, as anticipated, IPI-145 25 mg QD does not cause unanticipated toxicity in combination with FCR, a subsequent cohort will evaluate the full dose 25 mg bid dose. On the other hand, if unexpected toxicity is observed with IPI-145 25 mg QD, we will explore a lower dose of 15 mg QD, which has also been found to achieve serum concentrations that would be anticipated to be efficacious but may have less toxicity.

2.3 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 PI3K 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 lead to relapse, even in patients who initially respond well to therapy.

For older, less fit patients, utilizing a non-chemotherapy based strategy such as IPI-145 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 IPI-145, 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. Since younger patients 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 IPI-145 + FCR (iFCR) with the goal of achieving a more durable response, potentially even a cure. The side effect profiles of IPI-145 and FCR are generally non-overlapping, but given that this combination has not previously been explored, the current study includes an initial phase I 3+3 dose escalation cohort starting at 25 mg QD of IPI-145, which is below the single agent MTD of 25 mg bid being used in monotherapy studies. This phase Ib/II study of iFCR will evaluate the safety and efficacy of this combination in the upfront treatment of younger patients with CLL, with the primary objective of improving the rate of MRD-negative CR in the bone marrow in this patient population.

The primary objective of our study is to improve the rate of MRD-negative CR in the bone marrow in this patient population. From a theoretical perspective, 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 3 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 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.

Preliminary Results from Phase I

As of April 7, 2015, 12 subjects had been enrolled in the phase I portion of this trial. In the initial dosing cohort 1 (IPI-145 25 mg daily, 3 subjects), one subject experienced a DLT (febrile neutropenia), and therefore 3 additional subjects were accrued in cohort 1. None of the additional 3 subjects experienced a DLT, and therefore a dosing cohort 2 was opened (IPI-145 25 mg bid, 3 subjects). None of these three subjects experienced a DLT, and therefore 3 additional subjects were accrued in cohort 2 at 25 mg bid of IPI-145. None of these three additional subjects experienced a DLT. Since 0/6 subjects at 25 mg bid of IPI-145 in cohort 2 experienced a DLT, this dose was chosen as the recommended phase 2 dose, and will be the dose utilized in the phase II portion of this study.

2.4 Correlative Studies Background

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

We previously showed using primary CLL samples co-cultured with stroma *in vitro* that PI3K-delta inhibition can release CLL cells from stroma, and thereby increase priming for apoptosis (Davids et al., 2012). We also found that in a small, heterogeneously treated cohort of CLL patients, increased priming was associated with improved clinical response. 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.

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 and correlated with our primary endpoint of MRD-negative CR rate in the bone marrow. If we have positive bone marrow aspirates available, we will also perform BH3 profiling to see whether the level of priming in CLL cells from the marrow is a better predictor of response than the level of priming in peripheral blood CLL cells.

After 1 week of IPI-145 monotherapy, we will obtain a steady-state blood sample. We will compare the BH3 profile of this sample to a baseline sample, which will allow us to assess *in vivo* the short term change in apoptotic priming induced by IPI-145 as a single agent. BH3 profiling also has the ability to determine the relative dependence of CLL cells on anti-apoptotic proteins such as BCL-2, BCL-XL, and MCL-1. To determine whether anti-apoptotic dependence affects response, we will look to see whether patients who do not achieve an MRD-negative CR have a different pattern in their upfront BH3 profiles from those who do achieve MRD-negative CR. Finally, we will obtain peripheral blood and bone marrow samples from patients at the time of disease progression and look to see whether, compared to the baseline samples, apoptotic priming is decreased and/or the pattern of anti-apoptotic protein dependence has changed.

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, MYD88* and *SF3B1 (*Wang et al, 2011). At present, whether other recurrent mutations associate with prognosis is less clear, although our group also recently reported a shorter time to first therapy in patients carrying

mutations in NFKB pathway genes (Improgo et al, 2012), which could interact with sensitivity to IPI-145 depending on where in the pathway the mutations occur. 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 potential predictors of response and progression-free survival. We may 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

Pharmacodynamic markers will be assessed to determine how effectively IPI-145 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 and phospho-ERK compared to total AKT and ERK, 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.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

Unless otherwise specified, laboratory tests required for eligibility must be completed within 2 weeks prior to study entry. Baseline tumor measurements by CT scan (neck, chest, abdomen/pelvis), as well as bone marrow biopsy must be performed within 8 weeks of starting study treatment. Outside scans that are used for eligibility will need to be reviewed by the study team prior to registration.

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 CLL and an indication for treatment as per IW-CLL 2008 criteria

3.1.2 No prior therapy for CLL due to the patient's meeting IW-CLL 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 poorly tolerated in elderly subjects, persons > 65 years of age are excluded

3.1.4 ECOG performance status $\leq$1 (see Appendix A)

3.1.5 The effects of IPI-145 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

3.1.6 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 May not be receiving any other study agents

3.2.2 Patients with known CNS involvement are excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events

3.2.3 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris,

cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.4 Pregnant women are excluded from this study because IPI-145 has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with IPI-145, breastfeeding should be discontinued if the mother is treated with IPI-145. These potential risks may also apply to other agents used in this study

3.2.5 Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated with curative intent within the past 5 years: cervical cancer in situ, localized prostate cancer, and basal cell or squamous cell carcinoma of the skin

3.2.6 HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with IPI-145. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy

3.2.7 Inadequate hepatic function defined by aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >2.5 x upper limit of normal (ULN); direct bilirubin >1.5 x ULN unless due to hemolysis or Gilbert's syndrome

3.2.8 Inadequate renal function defined by serum creatinine >1.5 x ULN.

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

3.2.10 Concurrent treatment with any agent known to prolong the QTc interval (see Appendix E)

3.2.11 Patients with a history of active tuberculosis within the preceding two years.

3.2.12 Patients who have had a venous thromboembolic event (e.g., pulmonary embolism or deep vein thrombosis) requiring anticoagulation and who meet any of the following criteria:

- Have been on a stable dose of anticoagulation for <1 month
- Have had a Grade 2, 3 or 4 hemorrhage in the last 30 days
- Are experiencing continued symptoms from their venous thromboembolic event (e.g. continued dyspnea or oxygen requirement)

NOTE: Patients who have had a venous thromboembolic event but do not meet any of the above three criteria are eligible for participation

3.2.13 Patients with a history of alcohol abuse, chronic hepatitis, or other chronic liver disease (other than direct CLL liver involvement)
NOTE: Chronic hepatitis includes active infection with hepatitis B or C. All patients will be tested for hepatitis C virus antibodies (HCV Ab) and hepatitis B surface antigen (HBsAg) at screening. Patients with a positive result for HBsAg or HCV Ab will be excluded from enrolling in this study

3.2.14 Foods or medications that are strong or moderate inhibitors or inducers of CYP3A (see Appendix C) taken within 1 week prior to study treatment and for the duration of the study

3.2.15 Presence of active infection within 72 hours of treatment. 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

3.2.16 Significant co-morbid condition or disease which in the judgment of the Investigator would place the patient at undue risk or interfere with the study. Examples include, but are not limited to cirrhotic liver disease, sepsis, or recent significant traumatic injury.

3.2.17 Unable to receive prophylactic treatment for pneumocystis

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

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 Quality Assurance Office for Clinical Trials (QACT) 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.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. 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 must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

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

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT 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 protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed 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 QACT at 617-632-2295.

4. The QACT Registrar will (a) validate eligibility, and (b) register the participant on the study

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

4.3 General Guidelines for Other Participating Institutions

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

Following registration, participants should begin protocol treatment within 96 hours 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 must be changed. The Study Coordinator should be notified of participant status changes as soon as possible.

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

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 or emailed to the DFCI Study Coordinator (contact information on study contact list):

- Signed study consent form
- HIPAA authorization form
- Eligibility Checklist

The research nurse or data manager at the participating site will then call or email the DFCI Study Coordinator (contact information on study contact list) to verify eligibility. To complete the registration process, the Coordinator will:

- Register the participant on the study with QACT
- Fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration

Note: Registration and randomization with the QACT can only be conducted during the business hours of 8am – 5pm EST 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 IPI-145 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

In the phase Ib portion of the study, a standard 3 + 3 dose escalation will be performed, with IPI-145 starting at a dose of 25 mg QD. Patients will start with one week of IPI-145 monotherapy on cycle 1, day -7, and FCR will subsequently be introduced one week later on cycle 1, day 1, and administered at standard dosing for 6 cycles. Depending on the number of DLTs observed, escalation to IPI-145 25 mg bid or de-escalation to IPI-145 15 mg QD will be allowed. Once a recommended phase II dose (RP2D) is identified, the phase II expansion portion of the study will open using the RP2D plus FCR. At the conclusion of the portion of the study that includes FCR, responders will be allowed to continue on IPI-145 maintenance until time of progression for up to 2 years after completing FCR. If patients have discontinued IPI-145 but have continued to receive FCR on treatment, they may proceed to active follow-up for a period up to 2 years after completing FCR.

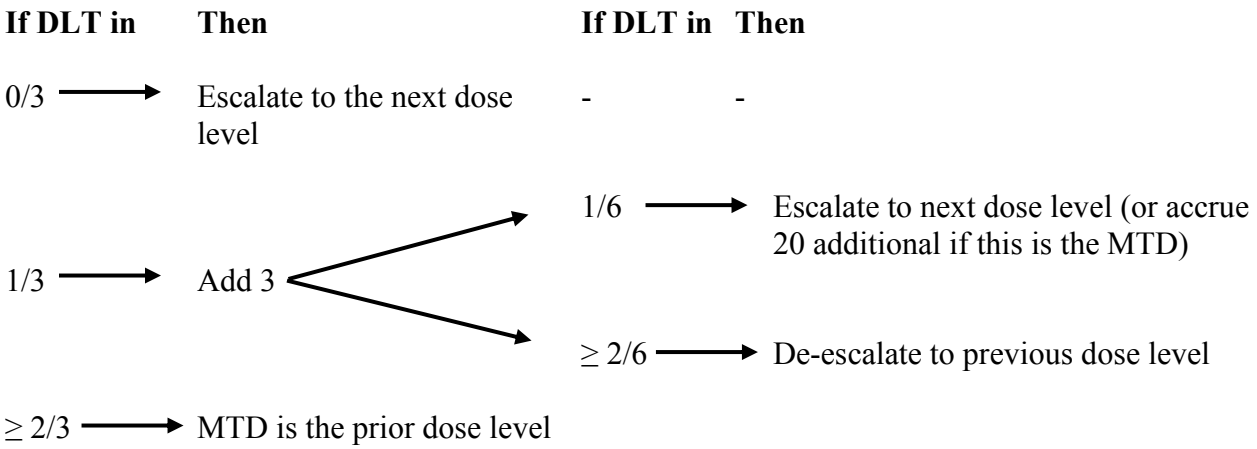
Table 2. Overview of Study Agents

iFCR				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
IPI-145	5 or 25 mg capsule	PO at same time(s) each day	QD or BID starting d-7, then continuous for 6 cycles and up to 2 yrs. maintenance	C1: 28 days plus 7 day lead in time(5 weeks) C2-6: 28 days (4 weeks)
Fludarabine*	25 mg/m^2	IV over approximately 30 to 60 min., given before rituximab unless clinically contraindicated	Days 1-3, week 1	
Cyclophosphamide*	250 mg/m^2	IV over approximately 30 to 60 min., given before rituximab unless clinically contraindicated	Days 1-3, week 1	
Rituximab	C1: 375 mg/m^2 C2-6: 500 mg/m^2	IV over protocol-mandated duration, given after FC unless clinically contraindicated	Day 1**, week 1	

** Fludarabine and cyclophosphamide may be dose-reduced beginning with cycle 1 as per standard of care at the discretion of the investigator, if approved by the PI. Standard dose*

reductions for fludarabine include reducing to 20 mg/m^2 or 15 mg/m^2 and for cyclophosphamide to 200 mg/m^2 or 150 mg/m^2.
***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.*

Dose escalation will proceed according to the following scheme:



Dose-Escalation Schedule **1 cycle = 28 days (except cycle 1 [28 days plus 7 day lead in])**		
	Dose Level	**Dose of IPI-145**
	2	**25 mg BID**
Starting Dose →	**1**	**25 mg QD**
	-1	**15 mg QD**

5.1 Pre-treatment Criteria

5.1.1 Cycle 1, Day 1

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

5.1.2 Subsequent Cycles

5.1.2.1 ANC must be ≥ 1000/mm3

5.1.2.3 Platelet count must be ≥ 75K or ≥100% of baseline

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

5.2 Agent Administration

In general, there is a +/- 4 day window for chemotherapy administration to allow for scheduling related issues.

5.2.2 Fludarabine

Fludarabine (commercial supply from various manufacturers) will be administered prior to rituximab unless clinically contraindicated. Fludarabine and cyclophosphamide may be administered either with fludarabine followed by cyclophosphamide or with cyclophosphamide followed by fludarabine, at the discretion of the treatment team. Fludarabine will be dosed at 25 mg/m2 on days 1, 2, and 3 of each 28 day cycle. Fludarabine may be dose reduced beginning with cycle 1 as per standard of care at the discretion of the investigator, if approved by the PI. Standard dose reductions for fludarabine include reducing to 20 mg/m^2 or 15 mg/m^2. 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 from the chemotherapy portion of the study. If they have completed at least 3 cycles of chemotherapy and have achieved a PR or better, they will be given the option of continuing on IPI-145 maintenance for 2 years or coming off study.

5.2.3 Cyclophosphamide

Cyclophosphamide (commercial supply from various manufacturers) will be administered prior to rituximab unless clinically contraindicated. Fludarabine and

cyclophosphamide may be administered either with fludarabine followed by cyclophosphamide or with cyclophosphamide followed by fludarabine, at the discretion of the treatment team. Cyclophosphamide will be dosed at 250 mg/m2 on days 1, 2, and 3 of each 28 day cycle. Cyclophosphamide may be dose reduced beginning with cycle 1 as per standard of care at the discretion of the investigator, if approved by the PI. Standard dose reductions for cyclophosphamide including reducing to 200 mg/m^2 or 150 mg/m^2.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. If they have completed at least 3 cycles of chemotherapy and have achieved a PR or better, they will be given the option of continuing on IPI-145 maintenance for 2 years or coming off study.

5.2.4 Rituximab

Rituximab will be administered after the chemotherapeutic agents unless clinically contraindicated. Rituximab from a commercial supply (Genentech, S. San Francisco, CA) will be administered IV at a dose of 375 mg/m^2 on day 1 of cycle 1. Patients with ≥ 15,000 circulating malignant cells/ mm^3 or at the discretion of the treating physician will receive only 50 mg/m^2 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 will receive allopurinol for tumor lysis syndrome prophylaxis with the first cycle.

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. Actual body weight measured at each treatment day will be used for calculations of body surface area. Patients with circulating disease ≥ 15,000 circulating malignant cells/mm^3 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 Dana-Farber Harvard Cancer Center institutional guidelines (please refer to section 7.1.3 for administration guidelines).

5.2.5 IPI-145

IPI-145 (Verastem, Needham, MA) will be administered orally once or twice per day in 28 day cycles (except for cycle 1, which is 28 days plus 7 day lead in). IPI-145 is administered orally as a capsule formulation and will be supplied free of charge by Verastem. IPI-145 will be administered as a fixed dose in mg/day and should be administered using the minimal number of capsules necessary. Starting on Cycle 1, Day -7, IPI-145 will be administered once a day or twice per day at the specified cohort dose. Doses must be taken within ±3 hours of the scheduled dose.

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(s) of day. 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.

IPI-145 capsules should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL) at approximately the same time(s) each day. Patients must avoid grapefruit or grapefruit juice. There are no restrictions with regard to fasting or fed state at the time of IPI-145 dosing.

5.3 Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) is based on the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

DLT refers to toxicities experienced at any time during the study treatment, defined as the following:

- Any Grade 3 or greater hematologic toxicity with exceptions for Grade 3 or Grade 4 neutropenia or thrombocytopenia that persists for ≤ 10 days off treatment.
- Any Grade 3 or greater non-hematologic toxicity with the following exceptions:
    - Grade 3 or greater nausea/vomiting/diarrhea despite optimal supportive care that persists for 7 days or less
    - Grade 3 infusion reactions
- Grade 3 asymptomatic laboratory abnormalities that improve to grade 2 or less within 3 days. Inability to receive day 1 therapy of Cycle 2 even after a three week treatment delay due to continued drug related toxicity from the prior cycle.
- Any Grade 4 or greater elevation in ALT/AST.

All toxicities will be considered relevant to determining DLT and to reporting unless the event can clearly be determined to be unrelated to the study drug(s).

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

Dose escalation will proceed within each cohort according to the following scheme:

Number of Subjects with DLT at a Given Dose Level Escalation Decision Rule: If there are 0 in 3 or ≤1 in 6 DLT at a given dose level then escalation will occur. If this is dose level 2 then this will be declared the RP2D

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 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 or Neupogen will be mandatory for all patients beginning with cycle 1. Neulasta will be administered at 6 mg SC x 1 on day 4 (or day 5 if necessary for scheduling reasons) of each cycle. Alternatively, Neupogen may be substituted at the discretion of the treating investigator and administered at 300-480mcg SC daily for up to 10 days, until ANC ≥ 1500 for two consecutive days. Neulasta and Neupogen will be from commercial supply.

5.4.2 Tumor Lysis Syndrome (TLS) Prophylaxis

Though relatively rare in CLL, tumor lysis syndrome (TLS), characterized by hyperkalemia, hyperuricemia, and hyperphosphatemia resulting from the rapid release of potassium, uric acid, and phosphate, has been reported in patients 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 IPI-145 monotherapy and continue through the end of cycle 1. 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 F) should receive vigorous intravenous hydration and should be considered for rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities. See Section 6.2, Dose Modification, for additional instructions.

5.4.2.1 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 4) should receive vigorous intravenous hydration and should be considered for rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities. See Section 6.2, Dose Modification Table, for additional instructions.

5.4.3 Prophylactic Antibiotics

Prophylaxis for Pneumocystis jiroveci pneumonia (PCP) with Bactrim or equivalent, and anti-herpetic viral prophylaxis with acyclovir or equivalent is mandated beginning with cycle one and continuing for the duration of the study.

5.4.4 CMV Monitoring:

Based on data from the IPI-145 phase I study in CLL, subjects taking IPI-145 might be at an increased risk of cytomegalovirus (CMV) reactivation. Clinically significant CMV infection can generally be avoided by close monitoring and institution of anti-CMV therapy at time of positive viral load detection. Therefore, all subjects on study will have mandatory CMV viral load measurement at study entry and monthly thereafter.

Subjects whose CMV viral load becomes positive will be started on valganciclovir 900 mg bid and the CMV viral load checked weekly until it becomes undetectable. At that point, dosing of valganciclovir can be changed to the prophylactic dose of 450 mg PO bid for the remainder of the study, but the subject should continue to undergo weekly CMV viral load surveillance for four consecutive negative tests, and can then return to monthly testing thereafter. Alternative anti-herpetic viral prophylaxis may be stopped during valganciclovir dosing.

Patients in the maintenance phase of the study can have CMV viral load testing performed every 2 months.

5.4.5 Medications that are Substrates of CYP3A4/5 or CYP2C8

In vitro studies in human liver microsomes have demonstrated IPI-145 is an inhibitor of cytochrome P450 (CYP) enzymes CYP2C8 (Ki = 1.1 μM) and CYP3A4/5 (Ki = 3.4 μM) activity, therefore systemic exposure to medications that are substrates for CYP2C8 or CYP3A4/5 may be increased in patients receiving IPI-145. The clinical significance of this inhibition is currently unknown; therefore, caution should be used if IPI-145 is used concomitantly with drugs or foods that are substrates of CYP2C8 and CYP3A4/5. Appendix B provides a list of medications known to be substrates of CYP3A4/5 or CYP2C8. Please note that Appendix B is not a comprehensive list of all medications which may be substrates of CYP3A4/5 or CYP2C8. The Principal Investigator should be contacted with any questions regarding concomitant use of medications that are CYP3A4/5 or CYP2C8 substrates.

5.4.6 Medications or Food that Inhibit or Induce CYP3A4/5

In vitro data also indicate that oxidative metabolism may play an important role in the elimination of IPI-145, with CYP3A4/5 identified as a primary contributor to drug metabolism. Draft data from a drug-drug interaction study with ketoconazole (a potent CYP3A4/5 inhibitor) indicate exposure to IPI-145 increased approximately 4- fold in the presence of ketoconazole. For this reason, the concomitant use of drugs or foods that are strong or moderate inhibitors or inducers of CYP3A are not allowed beginning 1 week prior to the first dose of IPI-145. Additionally, the use of these drugs and foods are not allowed during study treatment. Appendix C provides a list of medications known to be strong or moderate inhibitors or inducers of CYP3A. Please note that Appendix C is not a comprehensive list of all medications which may modulate CYP3A4/5 activity.

The Principal Investigator should be contacted with any questions regarding concomitant use of medications that are thought to modulate CYP3A activity. The concomitant use of weak inhibitors may be allowed in selected circumstances after consultation with the Principal Investigator.

5.4.7 Medications that are Substrates or Inhibitors of P-glycoprotein

In vitro data indicate that IPI-145 is a substrate for P-glycoprotein (P-gp). Concomitant medications that inhibit P-gp may cause the steady state concentration of IPI-145 to be reached more quickly than usual. These medications may be used as medically indicated but with caution. Additionally, *in vitro* studies demonstrated that IPI-145 has the potential to inhibit the active transport of other P-gp substrates. Appendix D provides a

list of medications that are substrates or inhibitors of P-gp. Please note that Appendix D is not a comprehensive list of all medications which may be substrates of P-gp or may modulate P-gp activity. The Principal Investigator should be contacted with any questions regarding concomitant use of medications that are thought to modulate P-gp activity.

5.5 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, treatment may continue for 6 cycles of combination therapy with iFCR with an additional 2 years of IPI-145 maintenance in responders, or until one of the following criteria applies:

- Disease progression
- 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.

5.6 Duration of Follow Up

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

5.7 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.5 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

Dose delays and modifications will be made using the following recommendations. Fludarabine and cyclophosphamide may be dose-reduced beginning with cycle 1 as per standard of care at the discretion of the investigator, if approved by the PI. Dose reductions of rituximab are not permitted in cycle 1. Patients who experience a DLT may stay on study with IPI-145 dosed at the next lower dose level, as per Table 3. In cycle 2 and beyond, dose reductions to fludarabine and/or cyclophosphamide will be made as per standard practices at the discretion of the treating investigator, after a discussion with the principal investigator. Dose reductions of rituximab will not be permitted.

Dose reductions of IPI-145 during cycles 2-6 and during the maintenance phase may be made as per table 3, after discussion with the principal investigator:

Table 3. IPI-145 Dose Reduction

Existing Dose (mg)	New Dose (mg)
25 mg PO bid	25 mg PO QD
25 mg PO QD	15 mg PO QD
15 mg PO QD	IPI-145 must be discontinued

Toxicity assessments will be done using the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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.

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.

6.1.2 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 and second malignancy, in particular developing cancers such as myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML). Further details may be found in the FDA-approved label and Micromedex.

6.1.3 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.

6.1.4 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.

6.1.5 Adverse Event List(s) for IPI-145

For a detailed description of the toxicology studies performed in animal models, please see section 2.2.2.

Frequently occurring (≥ 20% patients) adverse events observed in relapsed/refractory CLL/SLL patients receiving 25 mg BID included neutropenia (40%), diarrhea (32%), rash (combined terms) (32%), fatigue (28%), anemia (24%), ALT or AST increased (24%), cough (24%), pyrexia (24%), hyperglycemia (20%), nausea (20%) and sinus congestion (20%). Serious adverse events occurring in more than 1 relapsed/refractory CLL/SLL patient at 25 mg BID included febrile neutropenia (3 [12%]), disease progression (2 [8%]), and stomatitis (2 [8%]). Other notable serious events were infections, including upper respiratory infections and pneumonias.

Treatment-Related Lymphocytosis

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of IPI-145, in which inhibition of PI3K-mediated cellular homing

and adhesion results in a mobilization of tumor cells to the peripheral blood. Upon initiation of IPI-145 monotherapy, a rapid, but transient phase of increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5000/μL), often associated with reduction of lymphadenopathy, has been observed in the majority of patients with relapsed/refractory CLL/SLL treated with IPI-145. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings. Lymphocytosis occurs typically during the first few weeks of IPI-145 therapy, and resolves within a median of 6 months. In the case of this study, we expect a lymphocytosis to occur during the initial week of IPI-145 monotherapy, but this should resolve quickly over time as patients are treated with FCR.

Treatment of Overdose

In the case of overdose, clinic staff should be notified immediately and supportive care is to be given as indicated. Patients should be informed to contact their doctor immediately if they have taken an overdose and should stop taking IPI-145.

6.2 Dose Modifications/Delays

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 particular severity (see Table 4) at least possibly related to study drug, then dose modifications will be made according to Table 3. Deviations from these guidelines (e.g. drug interruption for Grade 2 pneumonitis/pneumonia or AST/ALT elevation) may occur only if approved by the principal investigator. There should be no attempt to make up for doses omitted due to toxicity.

Patients enrolled in the phase II expansion cohort or on maintenance who have an event which meets the DLT definition during any cycle will have IPI-145 withheld until resolution to Grade 1 or baseline. Upon resolution of the event, IPI-145 should be restarted at one dose level lower. In dose escalation patients, if the same event recurs during the subsequent cycle, the patient should be discontinued from the study. All IPI-145 dose reductions should be discussed with the principal investigator.

IPI-145 dosing may be withheld up to 28 days (up to 21 days for Cycle 1 only) for toxicity. Doses withheld for >28 days (> 21 days for Cycle 1 only) will result in discontinuation from the study. In cases where IPI-145 has been held >28 days, IPI-145 may be resumed after discussion with the overall PI in cases where toxicity is thought to be due to a cause other than IPI-145. Any patient who requires > 2 dose reductions for the same toxicity will be discontinued from the study. Patients who interrupt drug administration during Cycle 1 for a clinically significant drug-related AE that does not meet the DLT criteria will be considered to have had a DLT if the AE does not resolve to ≤ Grade 1 or baseline within 2 weeks.

For an individual patient, dose reductions and discontinuations may be more conservative than indicated in Table 4 and Table 5 (i.e., dose reduce or discontinue at a lower grade of non-hematologic toxicity) based on the clinical judgment of the investigator after discussion with the principal investigator.

Patients who have a dose reduction due to toxicity may be eligible for a dose increase back to the dose level prior to the reduction (i.e., the starting dose or dose of previous reduction if patient was dose reduced more than one level) if the following criteria are met:

1. Patient has tolerated the lower treatment dose for > 1 treatment cycle
2. Patient has recovered to baseline levels from the toxicity which caused the dose reduction

Table 4: Dose Modifications for IPI-145-Related Toxicities

IPI-145-related Toxicities[a, b]	**Dose Modification/Recommendation for IPI-145**[c]
Grade 1	Continue at current dose level
Grade 2	Continue at current dose level. If dose reduction is clinically indicated, contact the principal investigator
Grade 3 Hematologic	Continue at current dose level. If dose reduction is clinically indicated, contact the principal investigator

Grade 3 Nonhematologic (non-DLT)[d]	*First occurrence:* Withhold until return to Grade 1 or baseline level; re-initiate therapy at current dose level. If dose reduction is clinically indicated, contact the principal investigator *Second occurrence:* Withhold until return to Grade 1 or baseline level; re-initiate therapy at one dose level lower *Third occurrence:* Discontinue patient from study drug
Grade 3 Nonhematologic (DLT)[d]	*First occurrence:* Withhold until return to Grade 1 or baseline level; re-initiate therapy at one dose level lower. *Second occurrence:* Discontinue patient from study drug
Grade 4 Nonhematologic (other than asymptomatic lab abnormalities)	Discontinue patient from study drug
Grade 4 Hematologic (non-DLT)	*First occurrence:* Withhold until return to Grade 1 or baseline level; re-initiate therapy at current dose if duration ≤ 7 days. If duration >7 days, re-initiate therapy at one dose level lower. *Second occurrence:* Withhold until return to Grade 1 or baseline level; re-initiate therapy at one dose level lower. *Third occurrence:* Discontinue patient from study drug
Grade 4 Hematologic (DLT)	*First occurrence:* Withhold until return to Grade 1 or baseline level; re-initiate therapy at current dose if duration ≤ 3 days. If duration > 3 days, re-initiate therapy at one dose level lower. *Second occurrence:* Discontinue patient from study drug

a. IPI-145 Related = possible, probable, or definite relationship to IPI-145 as defined in Section 11.1.4.
b. Toxicity grades are defined per CTCAE Version 4.0. Note if parameter is not defined by CTCAE, then AE grading criteria (Section 11.1) should be utilized.
c. Refer to the beginning of section 6 for IPI-145 dose levels.
d. Includes Grade 3 diarrhea persisting for 7 days despite optimal antidiarrheal treatment, Grade 3 nausea and vomiting persisting for 7 days despite optimal antiemetic treatment, and Grade 3 QTcF prolongation. Grade 3 QTcF prolongation requires triplicate ECGs with the average measurement used and the use of Fridericia's correction method (QTcF). For patients with a right or left BBB, a Grade 3 QTc prolongation is defined as an increase in QTcF of >100 ms from the pre-dose ECG to any post-dose ECG as the QRS interval is prolonged at baseline (by approximately 40 ms) in patients with a BBB.

Table 5: Recommended IPI-145 Dose Reduction Levels

Dose (mg)	Reduction Level -1 (mg)	Reduction Level -2 (mg)
25 BID	25 QD	15 QD
25 QD	15 QD	Discontinue
15 QD	Discontinue	N/A

For patients enrolled in the phase II expansion cohort, a dose may be withheld up to 28 days for IPI-145-related toxicity. Doses withheld for >28 days due to IPI-145-related toxicity will result in discontinuation from the study. Any patient who requires >2 dose reductions due to treatment-related toxicity will be discontinued from the study.

Management Guidelines for Hepatotoxicity

Subjects who develop Grade 3 transaminase (ALT/AST) elevations with or without clinical symptoms should have IPI-145 held until return to baseline. IPI-145 may be reintroduced after lab values have remained at baseline levels for at least one week. Consideration may be given to resuming IPI-145 at a one dose level reduction. Additional work-up to evaluate viral infection/re-activation, exposure to environmental toxins (e.g., alcohol/con-meds), or other causes is recommended before restarting treatment with IPI-145.

If Grade 3 ALT/AST elevations recur upon re-challenge with IPI-145, hold IPI-145 and administer corticosteroids. In asymptomatic patients, a reduced dose of IPI-145 may be re-introduced after lab values have remained at baseline levels for at least one week.

IPI-145 will be discontinued permanently in subjects who experience Grade 3 ALT/AST elevations following 2 dose reductions or in subjects who experience Grade ≥4 ALT/AST elevations at any time. However, patients may remain on study and continue to receive FCR and subsequent active follow-up visits as outlined in the treatment schedule.

Dose Modification for FCR

Fludarabine and cyclophosphamide may be dose-reduced beginning with cycle 1 as per standard of care at the discretion of the investigator, if approved by the PI. Dose reductions due to toxicity from FCR will be made according to standard practice. Patients who meet DLT criteria for hematologic toxicity may for example 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 may be discussed with the PI including further dose reduction to 15 mg/m^2 for fludarabine and 150 mg/m^2 for cyclophosphamide. 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.

6.3 Stopping Rules

Adverse events will be monitored closely. The monitoring guidelines will serve as a trigger for consultation with the DF/HCC Data Safety and Monitoring Committee (DSMC) for additional review of potential closure of the study enrollment. The DSMC will automatically review this study every 6 months, but can review it at a shorter interval on an as needed basis (see section 12.2 for additional detail).

General Stopping Rule: If in the first 10 additional patients enrolled to phase II part, we observe 3 or more patients develop DLTs, further accrual to the phase II portion will be halted pending review by the DSMC. Depending on the findings of its review, the DSMC may recommend the permanent closure of enrollment or continuation of enrollment. As noted in section 5.3, the DLT observation period will include the entire duration of study treatment to capture any unacceptable toxicities that occur.

Stopping Rule for Hepatotoxicity: The observation period for hepatotoxicity will include the entire time the patient is on treatment. If in the first 7 additional patients (of the remaining 15 to be enrolled in the phase II portion) we observe 3 or more patients develop grade 3 or higher hepatotoxicity, further accrual to the phase II portion will be halted pending review by the DSMC. Depending on the findings of its review, the DSMC may recommend the permanent closure of enrollment or continuation of enrollment.

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 metabolize 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 IPI-145

7.2.1 Description

IPI-145 is a potent oral inhibitor of the delta- and gamma-isoforms of PI3K. In a phase I study of 117 patients with relapsed, refractory hematologic malignancies, pharmacokinetics studies revealed that IPI-145 is rapidly absorbed, with maximal plasma concentrations typically observed 1 hour following dosing (Patel, et al, 2013). Exposure (AUC) increased proportionally with doses through 75 mg PO bid. The half-life was 4-5 hours, regardless of dose. The mean pre-dose steady state plasma concentration following 25 mg BID was 390 ng/mL, indicating suppression of PI3K-delta (IC50=361 ng/mL) and PI3K-gamma (IC50=429 ng/mL) throughout the dosing interval. Pharmacodynamic studies confirmed rapid, profound and sustained inhibition of AKT phosphorylation by IPI-145 in CLL cells, as well as decreased levels of chemokines such as CCL3 and CCL4, which are important for lymphocyte trafficking. The MTD of IPI-145 as monotherapy for CLL has been determined to be 75 mg bid.

7.2.2 Form

IPI-145 drug substance is a white to off-white crystalline powder. The IPI-145 drug product is formulated with excipients (diluent/glidant, disintegrant, and lubricant) that are listed in FDA's Inactive Ingredients Database for approved drug products and/or Generally Regarded as Safe (GRAS). IPI-145 drug product is supplied as 5 mg (size 2 Swedish orange) and 25 mg (size 2 white hard) gelatin capsules for oral delivery.

7.2.3 Storage and Stability

IPI-145 must be stored at room temperature (15 to 30°C) and protected from light.

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 agent in a self-contained and protective environment.

Caution is required when handling IPI-145. 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 IPI-145 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 IPI-145 swallows a capsule or inhales drug powder from a broken capsule of IPI-145, 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

IPI-145 is an investigational agent and will be supplied free-of-charge from Verastem, Needham, MA.

7.2.7 Preparation

IPI-145 will be supplied to the clinical trial site as open-label medication. Capsules are packaged in opaque bottles with induction-sealed child-resistant caps or thermoform blister cards with peel and push child-resistant lidding. The label attached to each bottle or blister card will include, at a minimum, a statement limiting its use for investigational study only.

7.2.8 Administration

IPI-145 is administered orally as a capsule formulation once a day or twice per day in 28 day cycles as a fixed dose in mg, and should be administered using the minimal number of capsules necessary.

Beginning on Cycle 1, Day -7, IPI-145 will be administered QD or bid at the designated cohort dose, and will be administered in 28 day cycles (except for cycle 1, which is 28 days plus 7 day lead in). Doses must be taken within ±3 hours of the scheduled dose. 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. 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. IPI-145 capsules should be swallowed whole with a glass of water (approximately 8 ounces or 240 mL) at approximately the same time(s) each day. Patients must avoid grapefruit or grapefruit juice. IPI-145 may be administered without regard to meals. IPI-145 should be taken per the usual schedule on the days of laboratory correlative studies; administration should not wait until after procedures are performed.

7.2.9 Ordering

The DF/HCC pharmacy will order IPI-145 directly from Verastem, Needham, MA, who will be providing the study drug free of charge.

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 IPI-145 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

After full drug accountability and reconciliation, the Investigators will return all IPI-145 to Verastem, or its designee or, at Verastem's 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 IPI-145 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.

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

As the pharmacokinetic (PK) properties of IPI-145 have been well-characterized in patients with CLL, no additional PK studies are planned for this trial.

8.2 Pharmacodynamic Studies

8.2.1 Laboratory Correlative Studies

8.2.1.1 BH3 Profiling

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

We hypothesize that patients whose cells undergo significant depolarization to BIM BH3 peptide (highly primed) will have superior clinical response to 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 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 IPI-145 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 IPI-145 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, anothertube 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 at room temperature, where they will undergo Ficoll purification and then be viably frozen in FBS with 10% DMSO. The viably-frozen samples will be batched and later transported to the laboratory of Dr. Anthony Letai, where the BH3 profiling assays will be performed (for detailed methods see Ryan et al., 2010).

8.2.1.2 Genomic Analysis

We plan to perform whole exome sequencing on CLL cells and normal tissue from patients at baseline to evaluate for somatic mutations such as *NOTCH1, MYD88* 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 of the above samples will promptly be delivered to the laboratory of Dr. Jennifer Brown at room temperature, 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.

8.2.1.3 Pharmacodynamic Markers

Pharmacodynamic markers will also be assessed to determine whether IPI-145 is hitting its proposed target *in vivo*. Peripheral blood samples will be drawn pretreatment and 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 Verastem, who will use phosphoflow cytometry to determine the levels of phospho-AKT and phospho-ERK compared to total AKT and ERK, respectively. These analyses will 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.

8.2.1.4 Genzyme Minimal Residual Disease

Bone marrow samples will be collected for minimal residual disease analysis by Genzyme Genetics 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 months after combination therapy. Patients who have not already had Zap70, TP53 and IGHV testing

will send additional baseline samples to Genzyme/LabCorp. These samples will be shipped alongside the Integrated Oncology/LabCorp requisition form ambient priority overnight to:

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

8.2.1.5 Sample Collection Schedule

Sample Time Point	Container[1]	Sample Type	Shipping Method	Recipient[3]
Screening or Pre-dose Day -7	6x 6mL Green Top 1x6ml Red Top 1x10ml Purple Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
	1x6ml Green Top 1x3ml Purple Top	Bone Marrow Aspirate		
	1x Oragene Kit	Saliva[2]	Ambient overnight	
	2x10ml Purple Top* 1x6ml Green Top*	Peripheral Blood	Ambient overnight	Genzyme/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	Genzyme/LabCorp
Re-Staging (2 months post FCR)	6x6mL Green Top 1x6mL Red Top 1x10ml Purple Top	Peripheral Blood	Fridge pack overnight	CLL Center, J. Brown lab
	1x6ml Green Top 1x3ml Purple Top	Bone Marrow Aspirate		
	1x 6ml Green Top	Bone Marrow Aspirate	Ambient overnight	Genzyme/LabCorp
6 months post FCR	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	Genzyme/LabCorp
Q 6 months thereafter for up to 5 time points	6x6mL 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
[3]LabCorp and CLL labs only provides requisition form
* Samples required for all patients at baseline unless already been tested for Zap70, IGHV and TP53

9 STUDY CALENDAR

Baseline evaluations are generally to be conducted within 2 weeks prior to start of protocol therapy. Scans must be done ≤8 weeks prior to the start of therapy. Bone marrow biopsy must be done ≤8 weeks prior to the start of therapy unless done within the prior 6 months without intervening therapy. 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.

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 follow-up phase after the completion of the combination portion of the study, which may occur within a ±14 day window. The two month post FCR restaging visit may occur with a +14 day window.

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, amylase, beta-2 M
- Coagulation studies including prothrombin time and partial thromboplastin time
- Thyroid stimulating hormone level (TSH)
- Urinalysis
- Quantitative immunoglobulins and serum protein electrophoresis
- Direct antiglobulin test (Direct Coomb's test)
- Reticulocyte count
- Haptoglobin
- Bone marrow biopsy, including flow cytometry (lymphoma panel), karyotype, and FISH (CLL panel)
- Peripheral FISH analysis (if not being performed on Bone Marrow) (6 month window)
- CD4 panel (routine T-cell subsets)

- NOTCH1, MYD88 (unless already tested and enrolled on DFCI trial i.e: 99-224)
- Hepatitis B and C serologies
- HIV
- 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).
- Saliva Sample
- Baseline EKG
- Full body CT scan (neck, chest, abdomen/pelvis) with oral and IV contrast, unless contrast is contraindicated. Measurements will be made by the DF/HCC tumor imaging metric core (TIMC).
- Serum *IGHV* and *TP53* mutational analysis (1 purple top 10 cc tube each)and ZAP-70 testing (1 green top 6 cc tube) (unless already tested and enrolled on DFCI trial i.e: 99-224)

9.2 Evaluations During Treatment

9.2.1 The following assessments will be performed weekly during the first cycle, every 2 weeks during the second cycle, and on day 1 of all subsequent 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, amylase. AST/ALT and total bilirubin will be checked at least weekly in all subjects beginning in the third week of IPI-145 treatment and continuing through week 16 of IPI-145 treatment, even in the absence of abnormalities. Local laboratory testing will be acceptable at the discretion of the treating investigator, provided that the results can be obtained in a timely fashion.
- MRD performed on peripheral blood at cycle 3 re-stage.

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 assessments are to be performed within 7 days prior to completing cycles 3 and one month after completion of cycle 6 (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. Measurements will be made by the DF/HCC tumor imaging metric core (TIMC).
- A bone marrow biopsy will be performed to determine MRD status.

9.3 Evaluations after Combination Treatment

9.3.1 One Month Post-FCR Safety Evaluation

After completing FCR, patients will continue on IPI-145 with continuous dosing. They will be seen one month after FCR for a safety evaluation, and if continuing to tolerate IPI-145 well will continue on IPI-145 monotherapy thereafter.

The following clinical assessments will be performed at this visit:

- 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

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, total protein, and lactate dehydrogenase (LDH), direct bilirubin, amylase.

9.3.2 Two Months Post-FCR Re-staging Visit

For patients completing 6 cycles of therapy, restaging assessments should occur about 8 weeks after last dose of chemotherapy (+14 day window). 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 available, 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 at this visit:

- 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. Measurements will be made by the DF/HCC tumor imaging metric core (TIMC).

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, total protein, and lactate dehydrogenase (LDH), direct bilirubin, amylase.
- Bone Marrow Biopsy including flow cytometry and 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, ie 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.

9.3.3 IPI-145 Maintenance

Patients who complete 6 cycles of iFCR and have achieved a PR, CRi, or CR will be eligible to proceed with IPI-145 monotherapy as maintenance, and will continue at the same dose they were previously on during the combination portion of the trial. Patients who complete at least 3 cycles of iFCR but cannot receive additional cycles of chemotherapy due to toxicity will also be able to proceed to IPI-145 monotherapy maintenance, as long as they have achieved a PR, CRi, or CR.

All patients who go on to receive IPI-145 maintenance will be followed with visits every 2 months until time of progression for up to 2 years if there is no progression.

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 IPI-145 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 two month post-FCR CT scan and continued until disease progression, or for a minimum of 1 year if the disease remains in remission.

- 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 6 month intervals until MRD-negativity in both compartments is achieved is achieved
- For patients who have achieved MRD-negativity, serial MRD testing by flow cytometry will be performed every 6 months in the peripheral blood

9.3.4 Post-Maintenance Follow-up

Patients completing 2 years of maintenance IPI-145 or those who do not go on to receive IPI-145 maintenance will be followed on a schedule at the discretion of their oncologist until initiation of new therapy, or death. Patients who complete maintenance will have optional bone marrow biopsies yearly to assess for conversion to MRD-positive status.

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 IPI-145

- Restaging with full body CT 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 or for a minimum of 1 year if the disease remains in remission.

Study Calendar

	Pre-Study	C1D-7	C1D1	C1D2	C1D3	C1D8	C1D15	C1D22	C2D1	C2D15	C3-6 D1	1 month post FCR	2 months post FCR (re-staging)	Maintenance[k] (visits q 2 months)	30 day post-dose follow-up	Long Term Follow Up[n]	Off Treatment[d]
IPI-145		X----------												----------X			
FCR			X	X	X				X		X						
Informed consent	X																
History	X	X	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	X	X
Performance Status	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	X	X
Serum chemistry [a]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Descriptive Studies[b]	X																
CMV viral load[e]	X								X		X	X	X	X	X	X	X
B-HCG	X[c]																
EKG	X																
Bone Marrow Biopsy[j]	X										X		X	X	X	X	
MRD assessment[i]											X		X	X	X	X	X[g]
Radiographic evaluation[f]	X										X[f]		X		X	X	
Correlative studies[m]	X		X								X		X	X	X	X	X[h]
AE eval[l]				X----------													----------X

a: Albumin, alkaline phosphatase, direct bilirubin, total bilirubin, BUN, bicarbonate, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid. Lipase, and beta-2 M- only required at pre-study. AST/ALT and total bilirubin will be checked at least weekly in all subjects beginning in the third week of IPI-145 treatment and continuing through week 16 of IPI-145 treatment, even in the absence of abnormalities. Local laboratory testing will be acceptable at the discretion of the treating investigator, provided that the results can be obtained in a timely fashion.
b: Descriptive studies: Coagulation studies including prothrombin time and partial thromboplastin time; thyroid stimulating hormone level (TSH), urinalysis, quantitative immunoglobulins and serum protein electrophoresis, direct antiglobulin test (Direct Coomb's test), reticulocyte count, haptoglobin,CD4 panel (routine T-cell subsets), Hepatitis B and C serologies, NOTCH1, MYD88 and saliva.
c: Serum pregnancy test (women of childbearing potential).
d: Off-study evaluation should be conducted at each participating DF/HCC site, except in case of extenuating circumstances.
e: CMV viral load testing frequency in patients who develop a positive test will be increased to weekly until testing becomes negative, at which point testing can return to the schedule outlined here
f: Radiographic evaluations include CT neck/chest/abdomen/pelvis, and will occur at screening, at the conclusion of cycle 3, and at the re-staging visit 2 months after completing FCR.
g: For patients completing the full maintenance phase or those coming off study for reasons other than disease progression.
h: For patients coming off study due to disease progression.
i: MRD assessments will be performed by flow cytometry on both bone marrow and blood, just prior to cycle 4, at final re-staging visit, and then on blood only every 6 months during maintenance.
j: Bone marrow biopsy required pre-treatment, just prior to cycle 4, at 2 month post-FCR re-staging visit, and yearly thereafter in MRD-positive patients continuing on maintenance IPI-145
k: Please see section 9.3.4 for details on the post-maintenance follow-up schedule
l: IPI-145 should be taken per the usual schedule on the days of laboratory correlative studies; administration should not wait until after procedures are performed.
m: See section 8.2.1.5 for complete correlative study sample collection schedule.
n: Frequency of follow up visits and scans are per MD discretion. Recommended follow up visits for a minimum of one year. Treating physicians will notify lead site their preference for FU visits.

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 measurable disease present at baseline, 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 should be performed as closely as possible to the beginning of treatment and not more than 8 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. Head and neck tumors and those of extremities usually require specific protocols.

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 IPI-145 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 109/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, nonresponse, 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.

10.3.10 **Relapse**
Relapse is defined as a patient who has previously achieved the above criteria of a CR or PR, but after a period of 6 or more months, demonstrates evidence of disease progression.

10.3.11 **Refractory disease**
Refractory disease is defined as treatment failure or disease progression within 6 months to the last anti-leukemic therapy.

10.4 Response Review

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

11 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

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

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

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.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

For purposes of this protocol, grade 4 lymphopenia is considered an expected adverse event associated with study drugs. Such events will be recorded but not reported to the Principal Investigator or IRB.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 1 business day of learning of the occurrence. 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 1 business day 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)

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.4.2 Pregnancy Reporting

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study or within 30 days of the subject's last dose of study drug are considered immediately reportable events. IPI-145 is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence by facsimile or email.. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and the DF/HCC Overall Principal Investigator or designee must notify Verastem or designee immediately about the outcome of the pregnancy (either normal or abnormal outcome). If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the

Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Verastem or designee immediately by facsimile, or other appropriate method, within 1 business day of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Verastem or designee immediately by facsimile, or other appropriate method, within 1 business day of the Investigator's knowledge of the event using the SAE Report Form.

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study drug should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.4.3 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.

11.5 Reporting to Verastem

In parallel to reporting SAEs to the DF/HCC Overall Principal Investigator site-specific investigators must inform Verastem (or Verastem designee) in writing using a MEDWATCH 3500A form of any SAE within 1 business day of being aware of the event. The written report must be completed and supplied to Infinity by facsimile within 1 business day. Serious AEs should be communicated on the appropriate form as follows:

- fax number: 888-529-3580 (USA & Canada)
- email: rtpsafety@ppdi.com
- Hotline (Phone): 888-483-7729 (USA)

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. These updates and clarifications in follow-up reports will also be reported in parallel to the DF/HCC Overall Principal Investigator and Infinity. Event specific queries as well as monthly SAE listings to confirm receipt of all SAEs be sent directly from Infinity to the site specific PI, and the DF/HCC Overall Principal Investigator should be included on all such correspondence. A final report to document resolution of the SAE is required. At any time after completion of the AE reporting period (i.e., 28 days post-treatment), if an Investigator becomes aware of an SAE that is suspected by the Investigator to be related to IPI-145, the event must be reported as described above. A copy of

the fax transmission confirmation of all SAE reports to Infinity should be attached to the SAE and retained with the patient records.

11.6 Reporting to the Institutional Review Board (IRB)

Investigative sites will report all serious adverse events directly to the DF/HCC Office for Human Research Studies (OHRS).

11.7 Reporting to the Food and Drug Administration (FDA)

The Study Sponsor, as holder of the IND, will be responsible for all communication with the FDA. The Study Sponsor 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 as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA according to FDA reporting requirements using Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

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

N/A

11.9 Reporting to the Institutional Biosafety Committee (IBC)

N/A

11.10 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.

11.11 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 QACT will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

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 every 6 months 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.

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

N/A

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

N/A

14 STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

Study Design
An open-label, phase I/II study of IPI-145 in combination with fludarabine, cyclophosphamide, rituximab (iFCR) will be performed. The phase I part is a standard 3+3 design with three dose levels. Patients will start on day -7 with one week of IPI-145 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. FCR will subsequently be introduced on day 1, and administered at standard dosing for 6 cycles, with dose reductions permitted (see Section 6.2). Patients achieving either a PR or CR will be allowed to continue on IPI-145 maintenance for up to 2 years after completing chemotherapy. Conversion to MRD negativity and 2 year progression-free survival will be assessed for these patients.

Primary Endpoint:

- Safety of IPI-145 in combination with FCR in previously untreated younger patients with CLL
- Rate of minimal residual disease negative complete response (MRD-negative CR) in the bone marrow at 2 months post last cycle of FCR

Secondary Endpoints:

- Clinical response, including overall response rate, complete and partial response rates, progression-free survival, overall survival, and duration of remission as determined by 2008 IW-CLL criteria
- Rate of minimal residual disease (MRD) in the peripheral blood
- Rates of treatment-related adverse effects
- Association of established CLL prognostic factors (e.g. FISH cytogenetics, *IGHV* status, ZAP70 status) with clinical response

Exploratory Endpoints:

- BH3 profiling
- Change in pharmacodynamic markers such as p-AKT, p-ERK, and Ki-67
- Mutation status of *SF3B1, TP53, NOTCH1, MYD88* and the *BCR/NFKB* pathway

Phase I Design

Three doses of IPI-145 will be considered to determine MTD of IPI-145 in combination of FCR: 15 mg QD (dose level -1), 25 mg QD (dose level 1, starting dose), 25 mg bid (dose level 2). Dose limiting toxicities (DLTs) and the observation period are defined in section 5.3.

A cohort of 3 patients will enter at a dose level, starting dose level 1. If no DLT is seen in the first 3 patients, then a dose escalation will take place. If 2 or more of the first 3 patients experience

DLT at dose level 1 or 2, then the next cohort of 3 patients will be treated at the next lower dose level, unless 6 patients have already been treated at that dose level. If 2 or more of the first 3 patients experience DLT at dose level -1, then the study will be terminated early. If 1 of the 3 patients at a dose level experiences a DLT, then 3 additional patients will be treated at that dose level. If there is no DLT in the 3 additional patients then dose escalation will take place. If this is dose level 2 or -1, then this dose level will be the MTD. If 1 or more of the 3 additional patients experience(s) DLT then the MTD is considered to have been exceeded, and 3 more patients will be treated at the next lower dose, unless 6 patients have already been treated at that dose level. If this is does level -1, then the study will be terminated early. A minimum of six patients must be entered at the MTD, and fewer than 2 patients in 6 should experience DLT. If 0 in 6 patients experience DLT at dose level 2, this dose level will be the RP2D (recommended Phase II dose).

Table 1 shows the probability of escalation under various true DLT rates. With this design, there is 91% probability of escalation if the true but unknown rate of DLT is 10% and 17% probability of escalation if the rate is 50%.

Table 1. Probability of dose escalation

True but Unknown Rate of DLT	10%	20%	30%	40%	50%	60%
Prob. of Escalation	0.91	0.71	0.49	0.31	0.17	0.08

Phase II Design

The phase II part of the study is a single arm study which consists of determining the MRD-negative CR rate in the bone marrow at 2 months post IPI-145 + FCR in previously untreated CLL patients. An exact one sample binomial test is used to compute the sample size. Twenty additional patients will be enrolled and analyzed in conjunction with the 6 patients from the phase I portion treated at the MTD/RP2D for a total of 26 patients. Twenty-six patients are needed in order to detect a 45% MRD-negative CR rate, assuming the MRD-negative CR rate for the null hypothesis is 20% (Boettcher et al., 2012) and 90% power and 6% one-sided type I error. The null hypothesis will be rejected if 9 or more MRD-negative CRs are observed. Table 2 presents the operating characteristics of this design.

Table 2. Operating Characteristics

	True but Unknown Response Rate					
	20%	25%	30%	35%	40%	45%
Prob(≥9 responses)	0.06	0.18	0.37	0.59	0.77	0.90

14.2 Toxicity Monitoring.

Adverse events will be continuously monitored in the Phase II part of the study. The monitoring guidelines will serve as a trigger for consultation with the DF/HCC Data Safety and Monitoring Committee (DSMC) for additional review of potential closure of the study enrollment.

General Stopping Rule: If in the first 10 additional patients enrolled to phase II part, we observe 3 or more patients develop DLTs, further accrual to the phase II portion will be halted pending review by the

DSMC. Depending on the findings of its review, the DSMC may recommend the permanent closure of enrollment or continuation of enrollment. With this design, the probability of halting enrollment in the phase II portion is 0.07 if the true but unknown DLT is 10%, 0.62 if the rate is 30%, and 0.95 if the rate is 50%.

Stopping Rule for Hepatotoxicity: As of August 2015, grade 3/4 LFT elevations have been seen in 4/17 (24%): 1/6 at the dose level 1 and 3/11 at the dose level 2 (RP2D). If in the first 7 additional patients enrolled to phase II part, we observe 3 or more patients develop grade 3 or higher hepatotoxicity, further accrual to the phase II portion will be halted pending review by the DSMC. Depending on the findings of its review, the DSMC may recommend the permanent closure of enrollment or continuation of enrollment. With this design, the probability of halting enrollment after the additional 7 patients is 0.026 if the true but unknown grade 3/4 hepatotoxicity rate is 10%, 0.35 if the rate is 30%, 0.58 if the rate is 40%, and 0.77 if the rate is 50%.

14.3 Sample Size/Accrual Rate

Planned Sample Size: Minimum: 4, Maximum: 32
Estimated Monthly Accrual: 2-3
Follow-up: Patients completing 2 years of maintenance IPI-145 or those who do not go on to receive IPI-145 maintenance will be followed until initiation of new therapy, or death.

14.4 Stratification Factors

There will be no stratification of patients on this study.

14.5 Analysis of Secondary Endpoints

Clinical response, including overall response rate, complete and partial response rates determined by IW-CLL criteria as well as rate of MRD negativity in the peripheral blood will be summarized as percentages and 90% CI will be calculated using exact binomial test. The Kaplan Meier method will be used to summarize progression-free survival and overall survival descriptively. Association of established CLL prognostic factors (e.g. FISH cytogenetics, *IGHV* status, ZAP70 status) and clinical response will be assessed using Fisher's exact test for categorical variables and Wilcoxon's rank sum test for continuous variables. In addition, a correlation analysis between peripheral blood and bone marrow MRD negativity will be performed. Toxicity will be reported descriptively. Association between clinical outcome and exploratory endpoints will beevaluated. Exploratory endpoints include BH3 profiling, change in pharmacodynamic markers such as p-AKT, p-ERK, and Ki-67, and Genomic analysis with mutation status of *SF3B1, TP53, NOTCH1, MYD88* and the *BCR/NFKB* pathway.
Reporting and Exclusions

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

14.5.1 Evaluation of toxicity. All participants will be evaluable for toxicity from the time of their first treatment.

14.5.2 Evaluation of response. All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are

ineligible. Each participant will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 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.

16 REFERENCES

Barrientos JC, Furman RR, Leonard J, et al. Update on a phase I study of the selective PI3K-delta inhibitor idelalisib (GS-1101) in combination with rituximab and/or bendamustine in patients with relapsed or refractory CLL. *J Clin Oncol* 31, 2013 (suppl; abstr 7017).

Boettcher, S, Ritgen, M, Fischer, K, et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. *J Clin Oncol*, 2012, 30(9);980-8.

Brown, JR, Byrd, JC, Coutre, SE et al., Idelalisib, an inhibitor of phosphatidylinositol 3 kinase p110-delta, for relapsed/refractory chronic lymphocytic leukemia. *Blood*, 2014, Mar 10 [Epub ahead of print]

Byrd JC, Rai K, Peterson BL, Appelbaum FR, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. *Blood*. 2005 Jan 1;105(1):49-53. Epub 2004 May 11.

Ciraolo, E.; Morello, F.; Hirsch, E., Present and future of PI3K pathway inhibition in cancer: perspectives and limitations. *Curr Med Chem* 2011, *18* (18), 2674-85.

Davids MS, Brown JR. Phosphoinositide 3'-kinase inhibition in chronic lymphocytic leukemia. *Hematol Oncol Clin North Am*. 2013 Apr;27(2):329-39. doi: 10.1016/j.hoc.2012.12.002.

Davids, MS, Deng, J, Wiestner, A, et al. Decreased mitochondrial apoptotic priming underlies stroma-mediated treatment resistance in chronic lymphocytic leukemia, *Blood*, 2012, Oct 25;120(17):3501-9.

Flinn, IW, Patel, M, Kahl, BS, et al. Preliminary Safety and Efficacy of IPI-145, a Potent Inhibitor of Phosphoinositide-3-Kinase-δ,γ, in Patients with Chronic Lymphocytic Leukemia. ASH Annual Meeting, 2013, abstract 677.

Furman, R. R., Byrd, J.C., Brown, J.R., Coutre, S.E., Benson, D.M., et al., CAL-101, An Isoform-Selective Inhibitor of Phosphatidylinositol 3-Kinase P110d Demonstrates Clinical Activity and Pharmacodynamic Effects in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia. ASH Annual Meeting, 2010.

Hainsworth JD, Litchy S, Barton JH, et al., Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol*. 2003 May 1;21(9):1746-51

Hallek, M, Cheson, BD, Catovsky, D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood,* 2008, Jun 15;111(12):5446-56.

Hallek M, Fischer, K, Fingerle-Rowson, G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*, 2010, Oct 2;376(9747):1164-74.

Hoellenriegel, J.; Meadows, S. A.; Sivina, M., et al., The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leukemia. *Blood* 2011, *118* (13), 3603-12.

Improgo, MR, Kiezun, A, Wang, Y, et al. Functional Somatic and Germline Variants in the NF-KB Pathway in Chronic Lymphocytic Leukemia. ASH Annual Meeting, 2012.

Landau, DA, Carter, SL, Stojanov, P, et al. Evolution and Impact of Subclonal Mutations in Chronic Lymphocytic Leukemia. *Cell*, 2013, 152:714-726.

O'Brien SM, Kantarjian HM, Cortes J, et al. Results of the fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. *J Clin Oncol*. 2001 Mar 1;19(5):1414-20.

Patel M, Kahl B, Horwitz, SM, et al. Preliminary Safety and Efficacy of IPI-145, a Potent Inhibitor of Phosphoinositide-3-Kinase-δ,γ, in Patients with Relapsed/Refractory CLL. ASCO Annual Meeting, 2013, abstract 7070.

Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med*. 2000 Dec 14;343(24):1750-7.

Randis TM, Puri KD, Zhou H, Diacovo TG. Role of PI3Kdelta and PI3Kgamma in inflammatory arthritis and tissue localization of neutrophils. *Eur J Immunol*. 2008 May;38(5):1215-24.

Rawstron AC, Böttcher S, Letestu R, et al.; European Research Initiative in CLL. Improving efficiency and sensitivity: European Research Initiative in CLL (ERIC) update on the international harmonised approach for flow cytometric residual disease monitoring in CLL. *Leukemia*. 2013 Jan;27(1):142-9. doi: 10.1038/leu.2012.216. Epub 2012 Jul 31.

Subramaniam PS, Whye DW, Efimenko E, et al. Targeting nonclassical oncogenes for therapy in T-ALL. *Cancer Cell*. 2012 Apr 17;21(4):459-72.

Wang L, Lawrence, MS, Wan, Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. *N Engl J Med*, 2011, Dec 29;365(26):2497-506.

17 APPENDICES

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: Known CYP3A4 or CYP2C8 Substrates

The following lists provide known sensitive CYP3A4 substrates, CYP3A substrates with a narrow therapeutic range, and CYP2C8 substrates.

Additional information can be found at:
http://www.medicine.iupui.edu/clinpharm/ddis/ClinicalTable.asp and
http://www.pharmacytimes.com/issue/pharmacy/2008/2008-09/2008-09-8687

Sensitive CYP3A Substrates

budesonide
buspirone
eplerenone
eletriptan
felodipine
fluticasone
lovastatin
midazolam
saquinavir
sildenafil
simvastatin
triazolam
vardenafil

CYP3A Substrates with a Narrow Therapeutic Range

alfentanil
astemizole
cisapride
cyclosporine
diergotamine
ergotamine
fentanyl
pimozide
quinidine
sirolimus
tacrolimus
terfenadine

CYP2C8 Substrates

paclitaxel
torsemide
amodiaquine
cervistatin
repaglinide
rosiglitazone
pioglitazone

Appendix C: Medications or Foods Known to Inhibit or Induce CYP3A4

The following list provides medications known to induce or inhibit CYP3A activity. Note that this is not a comprehensive list of all medications which may modulate CYP3A activity.

Additional information can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm and
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#4

Classification of In Vivo Inhibitors of CYP3A Strong Inhibitors(1) ≥ 5-fold increase in AUC or > 80% decrease in CL	**Moderate inhibitors(2) ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL**	**Weak inhibitors(3) ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL**
Boceprevir, clarithromycin, conivaptan, grapefruit juice,(5) indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, (6) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, (5) imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, (4) goldenseal,(4) isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

1. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.
2. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
3. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.
4. Herbal product.
5. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
6. Withdrawn from the United States market because of safety reasons.

Classification of In Vivo Inducers of CYP3A

Classification of In Vivo Inducers of CYP3A Strong Inducers ≥ 80% decrease in AUC	**Moderate Inducers 50-80% decrease in AUC**	**Weak Inducers 20-50% decrease in AUC**
Avasimibe (1), carbamazepine, phenytoin, rifampin, St. John's wort(2)	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, Echinacea (3), pioglitazone, prednisone, rufinamide

1. Not a marketed drug.
2. The effect of St. John's wort varies widely and is preparation-dependent.
3. Herbal product.

Appendix D: P-gp Substrates and Medications that are Inhibitors of P-gp

The following list provides medications that are substrates or inhibitors of P-gp. This is not a complete list of all medications which may be substrates of P-gp or may modulate P-gp activity.

P-gp Substrates

Amitriptyline
Amiodarone
Atorvastatin
Cefoperazone
Chlorpromazine
Cimetidine
Ciprofloxacin
Clarithromycin
Colchicine
Cyclosporine
Dexamethasone
Digoxin
Diltiazem
Erythromycin
Estradiol
Fentanyl
Fexofenadine
Hydrocortisone
Itraconazole
Lansoprazole
Levofloxacin
Lidocaine
Loperamide
Losartan
Lovastatin
Methadone
Methotrexate
Methylprednisolone
Morphine
Nadolol
Norfloxacin
Nortriptyline
Ondansetron
Omeprazole
Pantoprazole
Phenytoin
Pravastatin
Propranolol
Quinidine
Ranitidine
Sirolimus
Tacrolimus
Timolol
Trimethoprim
Verapamil

P-gp Inhibitors

Amiodarone
Amitriptyline
Carvedilol
Chlorpromazine
Clarithromycin
Cortisol
Cyclosporine
Desimpramine
Diltiazem
Dipyridamole
Doxepin
Erythromycin
Felodipine
Fluphenazine
Grapefruit juice
Haloperidal
Itraconazole
Ketoconazole
Lovastatin
Mefloquine
Nicardipine
Nifedipine
Ofloxacin
Omeprazole
Pantoprazole
Progesterone
Propafenone
Propranolol
Quinidine
Rifampicin (Rifampin)
Saquinavir
Simvastatin
Sirolimus
Tacrolimus
Testosterone
Verapamil

Source: Atkinson AJ et al. Principles of Clinical Pharmacology, 2nd ed. cademic Press, Massachusetts, 2007.

Appendix E: Drugs Known to Prolong the QTc

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval. Medications that prolong the QT interval and/or have a risk of inducing Torsade de Pointes (TdP) are listed below. They are divided into two groups based on their known or perceived risk of causing TdP.

Additional information can be found at: http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm

Group 1. Drugs that are Generally Accepted by Authorities to have a Risk of Causing Torsades de Pointes

Group 1 Drugs

Amiodarone	Ibutilide
Arsenic trioxide	Levomethadyl
Bepridil	Mesoridazine
Chlorpromazine	Methadone
Chloroquine	Moxifloxacin
Cisapride	Pentamidine
Disopyramide	Pimozide
Dofetilide	Probucol
Domperidone	Procainamide
Droperidol	Quinidine
Erythromycin	Sotalol
Halofantrine	Sparfloxacin
Haloperidol	Thioridazine
	Vandetanib

Group 2. Drugs That in Some Reports May be Associated With QT Prolongation and/or Torsades de Pointes But at This Time Lack Substantial Evidence of Causing Torsades de Pointes

Group 2 Drugs

Alfuzocin	Nicardipine
Amantadine	Nilotinib
Atazanavir	Octreotide
Azithromycin	Ofloxacin
Chloral hydrate	Ondansetron
Clozapine	Oxycontin
Dolasetron	Paliperidone
Dronedapone	Quetiapine
Escitalopram	Ranolazine
Felbamate	Risperidone
Flecainide	Roxithromycin
Foscarnet	Sertindole
Fosphenytoin	Sunitinib
Gatifloxacin	Tacrolimus
Gemifloxacin	Tamoxifen
Granisetron	Telithromycin

Indapamide	Tizanidine
Isradipine	Vardenafil
Lapatinib	Venlafaxine
Levofloxacin	Voriconazole
Lithium	Ziprasidone
Moexipril/HCTZ	

Appendix F: Cairo-Bishop Tumor Lysis Syndrome Criteria

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

Appendix G NCI CTC Version 4.0

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 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.