PROTOCOL

TITLE:	A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
PROTOCOL NUMBER:	PCYC-1112-CA
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
EUDRACT NUMBER:	2012-000694-23
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PROTOCOL APPROVAL PAGE

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Study Number: PCYC-1112-CA

Protocol Date: 01 March 2012

Amendment 1 Date: 28 September 2012

Amendment 2 Date: 13 December 2012

Amendment 3 Date: 08 August 2013

Amendment 4 Date: 24 September 2013

Amendment 5 Date: 16 January 2014

Amendment 6 Date: 27 October 2014

Amendment 7 Date: 28 September 2016

I have carefully read Protocol PCYC-1112-CA entitled "A Randomized, Multicenter, Open Label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma." I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics. All data pertaining to this study will be provided to Pharmacyclics. The policy of Pharmacyclics, LLC requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Pharmacyclics, LLC representative is authorized to sign the protocol and any amendments:

10 Oct 2016

Medical Monitor's Signature Date
George Cole, M.D.
Clinical Development, Pharmacyclics, LLC.

SYNOPSIS

Study Title:	A Randomized, Multicenter, Open-Label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
Protocol Number:	PCYC-1112-CA
Study Phase:	3
Study Duration:	Estimated to be approximately 6 years
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as hard gelatin capsules for oral (PO) administration. Note: "PCI-32765" and "ibrutinib" refer to the same molecule; hereafter, "ibrutinib" will be used. Ofatumumab will be supplied as a liquid concentrate (20 mg/mL) to be diluted for intravenous (IV) administration.
Objectives:	**Primary Objective:** To evaluate the efficacy of ibrutinib compared to ofatumumab based on independent review committee (IRC) assessment of progression-free survival (PFS) per International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL, Hallek 2008) with incorporation of the clarification for treatment related lymphocytosis (Hallek 2012) (hereafter referred to as IWCLL 2008 criteria) in patients with relapsed or refractory CLL/SLL. **Secondary Objectives**: *Efficacy* To compare efficacy between the two treatment groups in terms of: • To evaluate overall survival (OS) • To evaluate IRC-assessed overall response rate (ORR) per IWCLL 2008 criteria • To evaluate patient-reported outcome (PRO) by FACiT-Fatigue • To evaluate hematological improvement *Safety* • To evaluate the safety and tolerability of ibrutinib compared to ofatumumab **Exploratory Objectives:** • To evaluate Investigator-assessed PFS and ORR per IWCLL 2008 criteria • To evaluate improvement and/or resolution of disease-related symptoms • To evaluate PRO by EORTC QLQ-C30 and EQ-5D-5L • To evaluate medical resources utilization (MRU)

	• To determine the pharmacokinetic (PK) characteristics of ibrutinib in patients with CLL/SLL • To investigate predictive biomarkers and mechanism of resistance
Study Design:	This is a randomized, multicenter, open-label, Phase 3 study designed to compare the efficacy and safety of ibrutinib versus ofatumumab in patients with relapsed/refractory CLL or SLL with active disease requiring treatment (as defined by IWCLL 2008 criteria for initiation of therapy) who have failed at least 1 prior line of therapy and are not appropriate candidates for treatment or retreatment with purine analog based therapy. Eligible patients will be randomized in a 1:1 ratio into 2 arms to receive either IV ofatumumab (Treatment Arm A) per package insert or ibrutinib (Treatment Arm B) 420 mg daily until disease progression, unacceptable toxicity, or criteria specified in Section 10.1, whichever occurs first. Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, patients will be randomized based on the following two stratification factors: disease refractory to purine analog and anti-CD20 containing chemoimmunotherapy regimen, and the deletion 17p13.1 (17p del). The stratified analysis will be performed based on these two randomization stratification factors. Assessment for tumor response and progression will be conducted in accordance with the IWCLL 2008 criteria for patients with CLL and SLL until progressive disease with the modification that isolated treatment-related lymphocytosis will **not** be considered as disease progression as recommended by the IWCLL 2008 guideline clarification (Hallek 2012) and the National Comprehensive Cancer Network (NCCN), 2012 guidelines and further defined in Section 6.2.5. Access to next-line ibrutinib for patients treated with ofatumumab may be provided with Medical Monitor approval as outlined in Section 7.3.4. Patients will be followed for survival and use of anticancer agents until study closure. The study will end approximately 5 years after the last patient is enrolled, at which time a long-term extension study will be made available for patients who choose to continue ibrutinib on a clinical protocol when access to commercial ibrutinib is not feasible. An independent data monitoring committee (DMC) will monitor the safety of the study.
Population:	Patients with CLL or SLL who have failed at least 1 prior line of therapy and are not considered appropriate for treatment or retreatment with purine analog based therapy.
Centers:	Multicenter – International
Key Inclusion Criteria: *Refer to Section 5 for the complete and detailed list of inclusion/exclusion criteria.*	• Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. • Diagnosis of CLL or SLL that meets IWCLL 2008 criteria. • Active disease meeting at least 1 of the IWCLL 2008 criteria for requiring treatment.

	• Must have received at least one prior therapy for CLL/SLL. • Must not be appropriate for treatment or retreatment with purine analog based therapy. • Measurable nodal disease by CT. • Must have the following laboratory parameters met for inclusion: ▪ Absolute neutrophil count (ANC) ≥ 750 cells/μL (0.75×10^9/L), independent of growth factor support. ▪ Platelet count ≥ 30,000 cells/μL (30×10^9/L) without transfusion support. ▪ Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) < 2.5 x upper limit of normal (ULN). ▪ Total bilirubin ≤ 1.5 x ULN. ▪ Estimated creatinine clearance (ie, estimated Glomerular Filtration Rate, eGFR) using Cockcroft-Gault ≥ 30 mL/min. • Patient must be able to receive outpatient treatment and laboratory monitoring at the institution that administers study drug for the entire study.
Key Exclusion Criteria:	• Known central nervous system (CNS) lymphoma or leukemia. • Known prolymphocytic leukemia or history of or currently suspected Richter's transformation. • Missing or incomplete documentation of cytogenetic and/or FISH results reflecting presence or absence of 17p del and the percentage of cells with the deletion in patient records prior to randomization. • Uncontrolled autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP). • Prior exposure to ofatumumab or to ibrutinib (PCI-32765) or randomization into an ibrutinib study. • Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days prior to first dose of study drug. • Corticosteroid use > 20 mg within 1 week prior to first dose of study drug. • Radio- or toxin-conjugated antibody therapy within 10 weeks prior to first dose of study drug. • Prior autologous transplant within 6 months prior to first dose of study drug. • Prior allogeneic stem cell transplant within 6 months or with any evidence of active graft versus host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug. • History of major surgery within 4 weeks prior to first dose of study drug. • History of prior malignancy, with specific exceptions

	• Currently active clinically significant cardiovascular disease or history of myocardial infarction within 6 months prior to first dose of study drug. • Known history of infection with human immunodeficiency virus (HIV). • Serologic status reflecting active hepatitis B or C infection. • Unable to swallow capsules or disease significantly affecting gastrointestinal function. • Uncontrolled active systemic fungal, bacterial, viral, or other infection. • History of stroke or intracranial hemorrhage within 6 months prior to randomization. • Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug. • Requires treatment with a strong CYP3A4/5 inhibitor.
Primary Endpoints:	The primary endpoint of this study is PFS, as assessed by IRC review per IWCLL 2008 criteria.
Secondary and Exploratory Endpoints:	Secondary Endpoints: *Efficacy* To compare efficacy between the two treatment groups in terms of: • OS. • ORR defined as the proportion of patients who achieve a response (assessed by the IRC per IWCLL 2008 criteria). • PRO as measured by FACiT-Fatigue. • Hematological improvement in the subset of patients with cytopenia(s) at baseline assessed by time to and percentage of patients with improvement in blood counts. *Safety* • To compare the safety and tolerability between the two treatment groups. Exploratory Endpoints: • Investigator-assessed PFS per IWCLL 2008 criteria. • Investigator-assessed ORR per IWCLL 2008 criteria. • Improvement and/or resolution of disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain due to splenomegaly, or anorexia). • PRO as measured by EORTC QLQ-C30 and EQ-5D-5L. • MRU associated with the therapy including the number of hospitalizations, emergency department visits, blood product transfusions, and use of hematopoietic growth factors. • PK characteristics of ibrutinib in patients with relapsed or refractory CLL/SLL.

	• Exploratory analyses based on predictive biomarkers and/or mechanisms of resistance.
Study Treatment:	**Treatment Arm A: Ofatumumab** Refer to ofatumumab package insert for more details. **Premedication** Premedication should be administered per the ofatumumab package insert. **Dosing/Administration** The ofatumumab dosage and schedule is 12 doses administered over 24 weeks or until disease progression, unacceptable toxicity, or criteria specified in Section 10.1: Week 1: 300 mg initial dose Week 2 through 8: 2,000 mg (once weekly) Week 12, 16, 20 and 24: 2,000 mg (every 4 weeks) Ofatumumab should be administered as an intravenous (IV) infusion without bolus. Please see infusions guidelines in Section 6.1.1. Following Medical Monitor approval ibrutinib can be administered as salvage therapy as outlined in Section 7.3.4. **Treatment Arm B: Ibrutinib** Ibrutinib 420 mg (3 x 140-mg capsules) will be administered orally once daily until disease progression, unacceptable toxicity, or criteria specified in Section 10.1.
Concomitant Therapy:	*Refer to Section 6.6 for information on concomitant therapy.*
Safety Plan: *Refer to Section 9.1 and DMC charter for details.*	The safety of this study will be monitored by an independent DMC in accordance with the Sponsor's Pharmacovigilance Committee procedures.
Statistical Methods and Data Analysis:	All efficacy analyses will be performed using the intent-to-treat (ITT) population. All the stratified analyses will be based on the two randomization stratification factors: 1) refractory disease (presence versus absence) to purine analog and anti-CD20 containing chemoimmunotherapy regimen, and 2) status of 17p del (presence versus absence). **Primary Efficacy Analysis:** PFS as determined by the IRC will be summarized for each treatment arm using Kaplan-Meier estimates and compared using stratified log rank test. **Secondary Efficacy Analysis:** Overall response rate (ORR) as determined by the IRC will be compared using the Cochran-Mantel-Haenszel chi-square test, stratified by the two stratification factors (refractory disease and 17p del). Overall survival will be compared using stratified log rank test. Survival rate at landmark points will be summarized based on Kaplan-Meier point estimates and compared using the standard normal Z test.

	Descriptive statistics for change in scores from baseline to each assessment will be summarized for the PROs assessed by the FACiT-Fatigue. Time to hematological improvement will be compared using unstratified log rank test. Percentage of patients achieving hematological improvement will be compared using the chi-square test. **Exploratory Efficacy Analysis:** PFS and ORR as determined by the Investigator will be summarized and analyzed similarly to PFS and ORR as determined by the IRC. Percentage of patients achieving improvement/or resolution in disease-related symptoms will be compared using chi-square test. Descriptive statistics for change in scores from baseline to each assessment will be summarized for the PROs assessed by EORTC QLQ-C30 and EQ-5D-5L. Descriptive statistics will be provided for parameters collected for medical resource utilization associated with the therapy. **Safety Analysis:** Detailed tabulations of safety data (adverse events [AEs] and clinical laboratory tests) will be provided for all patients receiving the study drug. The number and percent of patients with treatment-emergent AEs will be summarized. Summary of other safety parameters by treatment group will be provided where appropriate.
Interim Analysis	One interim analysis using the Lan-DeMets alpha spending function based on O'Brien-Fleming boundary for both superiority and futility (non-binding) will be conducted after observing approximately 117 PFS events. Futility will be evaluated by a one-sided test. The DMC will review and evaluate efficacy and safety results.
Sample Size Determination	With the agreement from the European (Rapporteur and Co-Rapporteurs) and US Health Authorities, the overall two-sided significance level for this study is revised from 0.01 to 0.05. Given this revision in overall significance level, 176 PFS events provides approximately 90% power to detect the target hazard ratio of 0.6 based on a log-rank test and a two-sided overall significance level of 0.05 adjusted for one planned interim analysis.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations

17p del	chromosome deletion 17p13.1
AE(s)	adverse event(s)
AIHA	autoimmune hemolytic anemia
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BFR	bulky fludarabine-refractory
BR	bendamustine/rituximab
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CD20	cluster of differentiation 20
CDC	complement dependent cytotoxicity
CFR	Code of Federal Regulations
CIRS	Cumulative Illness Rating Score
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete remission (response)
CrCl	creatinine clearance
CRF	case report form
CRi	CR with incomplete bone marrow recovery
CSSR	Clinical Supplies Shipping Receipt Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450

Abbreviations

Cys	Cysteine residue
DLBCL	diffused large B-cell lymphoma
DMC	Data Monitoring Committee
DR	double refractory
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EMR	electronic medical records
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	Euro-QoL five dimension
ESMO	European Society for Medical Oncology
FACiT-Fatigue	The Functional Assessment of Chronic Illness Therapy-Fatigue
FCR	fludarabine/cyclophosphamide/rituximab
FcγR	Fc-gamma receptors
FDA	Food and Drug Administration
FISH	fluorescence *in situ* hybridization
GCSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HDPE	high-density polyethylene
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgVH	immunoglobulin heavy-chain variable
ILD	interstitial lung disease

Abbreviations

INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
ITP	idiopathic thrombocytopenic purpura
ITT	Intent-to-treat
IV	Intravenous
IVIG	intravenous immune globulin
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LDT	lymphocyte doubling time
LN	lymph node
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRU	medical resources utilization
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
nPR	nodular partial remission (response)
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PO	per os (oral)
PR	partial remission (response)
PRO	patient reported outcome

Abbreviations

PT	prothrombin time
QLQ-C30	Quality of Life Questionaire Core 30
QTc	corrected QT interval
REB	Research Ethics Board
RS	Richter's syndrome
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SCARs	severe cutaneous adverse reactions
SD	stable disease
SI	standard international units
SJS	Stevens-Johnson Syndrome
SLL	small lymphocytic lymphoma
SOC	system organ class
SOP	standard operating procedures
SPD	sum of the product of the diameters
T_{max}	time to maximum drug concentration
TLS	tumor lysis syndrome
ULN	upper limit of normal
USP	United States pharmacopeial convention
ZAP-70	Zeta-chain-associated protein kinase 70

1. INTRODUCTION

Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL) are a malignancy of B-cells that predominantly affects the older population. Chemoimmunotherapy, in particular the combination of purine analogs (eg, fludarabine) with cyclophosphamide and rituximab, has become a standard for the treatment of young and/or fit individuals with CLL who require treatment. However, elderly patients and those with comorbidities are often unable to tolerate combination chemoimmunotherapy regimens, or experience inferior clinical outcomes when treated with these regimens. In addition, those patients who have a deletion in the short arm of chromosome 17p13.1 (17p del) and/or those who fail to achieve a response or experience short remissions to purine analog based therapies have inferior outcomes and may prove to be refractory to therapy and/or experience short remission durations and rapid progression of disease when treated with standard and currently available treatment regimens.

The generation and maintenance of normal and malignant B-cells is controlled by biochemical signals transmitted by the B-cell receptor (BCR). Bruton's Tyrosine Kinase (BTK) is an enzyme required for BCR signaling. Selective BTK inhibition is a novel approach to target diseases driven by BCR activation, such as B-cell lymphoma and leukemia.

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of BTK co-developed by Pharmacyclics LLC and Janssen Research & Development LLC for the treatment of B-cell malignancies.

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

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure (IB).

1.1. Ibrutinib

"Ibrutinib" and "PCI-32765" refer to the same molecule; hereafter, "ibrutinib" will be used. Ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo [3, 4 d] pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib is a white to off-white crystalline solid. It has a single chiral center and is the R-enantiomer. The investigational drug product, ibrutinib, is an oral formulation containing micronized ibrutinib.

1.1.1. Mechanism of Action of Ibrutinib

Ibrutinib binds covalently to a cysteine residue (Cys-481) near the BTK active site and inhibits the enzymatic activity of purified BTK with a half maximal inhibitory concentration (IC_{50}) of 0.5 nM (Honigberg 2010; Pan 2007). Covalent binding to Cys-481 results in irreversible inhibition of BTK. Other kinases that are potentially inhibited by ibrutinib have been identified using an Ambit kinome screen. The inhibitory effect of ibrutinib against the activity of these kinases has been characterized in biochemical assays. Only a small subset of kinases is predicted to contain a modifiable cysteine residue homologous to Cys-481 in BTK, and thus have the potential to be irreversibly modified by ibrutinib. The other Cys-481 containing kinases include EGFR (IC_{50} = 12 nM), HER2 (IC_{50} = 22 nM), HER4 (IC_{50} = 0.6 nM), ITK (IC_{50} = 12 nM), BMX (IC_{50} = 1 nM), JAK3 (IC_{50} = 22 nM), and BLK (IC_{50} = 1 nM).

A fluorescently-tagged derivative of ibrutinib was shown to bind predominantly to BTK in B-cell lysates suggesting a high degree of specificity within B-cells (Honigberg 2010). Ibrutinib also has reversible inhibitory activity against other kinases that do not contain Cys-481 (Honigberg 2010). However, assuming a rapid off-rate, any reversible kinase inhibition *in vivo* is likely to be short-lived, since, in humans, the effective half-life of ibrutinib following oral dosing is only 1.5 to 3.3 hours (as measured from time of maximum drug concentration [T_{max}] to 6 hours postdose).

Thus, by combining fast irreversible binding to BTK with rapid *in vivo* elimination, ibrutinib provides a unique approach to improve selectivity for BTK *in vivo* relative to reversibly inhibited off-target kinases.

1.1.2. Cellular Selectivity of Ibrutinib

BTK expression is limited to cells of hematopoietic origin. The cellular selectivity of ibrutinib was demonstrated by the observation that ibrutinib inhibits antigen-receptor signaling in B-cells, but not in T-cells. In *ex vivo* stimulation assays, ibrutinib inhibits human BCR activation (IC_{50} <10 nM) in B-cells, but does not affect T-cell receptor activation (Honigberg 2010). It has also been confirmed that ibrutinib inhibits key phosphorylation events downstream of the BCR at similar concentrations. Ibrutinib has been studied in other cell types where the function of BTK is understood, including mast cells, basophils, monocytes, macrophages, and platelets. Consistent with the functional role of BTK in mast cells and basophils, Pharmacyclics determined that ibrutinib fully inhibits degranulation following stimulation at the high-affinity Immunoglobulin E (IgE) receptor (MacGlashan 2011; Chang 2011a). In monocytes and macrophages, ibrutinib inhibits the secretion of pro-inflammatory cytokines following stimulation at the Fc-gamma receptors (FcγR) by immune complex (Chang 2011a). Consistent with the proposed function of BTK in platelets, unpublished data from Pharmacyclics also shows that ibrutinib inhibits shear-force and collagen-induced platelet aggregation *in vitro* (IC_{50} = 10-100nM).

1.2. Summary of Nonclinical Data

For more detailed and comprehensive information of ibrutinib, please refer to the Investigator's Brochure (IB).

1.2.1. Nonclinical Pharmacology Studies

Ibrutinib was designed as a selective and covalent inhibitor of the BTK protein (Pan 2007). *In vitro*, ibrutinib is a potent inhibitor of BTK activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to Cys-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the BCR and blocks activation of B-cells (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

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

1.2.2. Safety Pharmacology and Toxicology

No treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs. Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog). In studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals. Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

1.3. Summary of Clinical Data

1.3.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally with substantial intersubject variability. The mean terminal plasma elimination half life ($t_{1/2}$) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Despite the doubling in mean systemic exposure when dosed with food, the favorable safety profile of ibrutinib allows dosing with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of the main metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure implying non-clinically relevant accumulation. Less than 1% of ibrutinib is excreted in the urine. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

For the most comprehensive information regarding pharmacokinetics (PK) and product metabolism, please refer to the current version of the IB.

1.3.2. Clinical Studies

As of 4 October 2011, over 300 patients with various B-cell malignancies have received ibrutinib in six clinical studies sponsored by Pharmacyclics. A total of 133 patients with CLL or SLL have received single-agent ibrutinib across two clinical studies: PCYC-04753 in patients with recurrent B-cell lymphoma (including 16 CLL/SLL patients) and a Phase 1b/2 study (PCYC-1102-CA) in patients with CLL/SLL (n=117). Two Phase 1b/2 studies are ongoing to evaluate the safety and efficacy of ibrutinib in combination with chemoimmunotherapy or CD20 monoclonal antibody therapy in relapsed or refractory CLL/SLL patients, specifically with bendamustine/rituximab (BR) and fludarabine, cyclophosphamide, and rituximab (FCR) in Study PCYC-1108-CA, and with ofatumumab in Study PCYC-1109-CA.

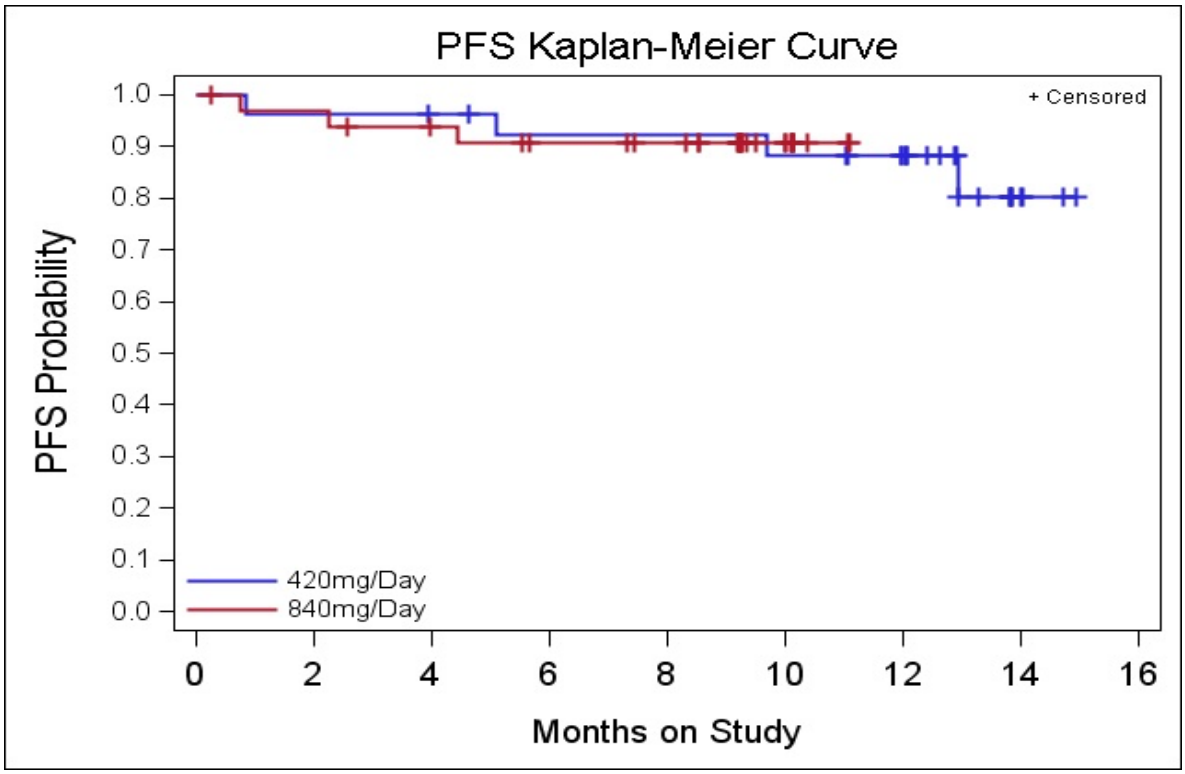
Additional clinical studies of ibrutinib in other B-cell malignancies, specifically mantle cell lymphoma (MCL), diffused large B-cell lymphoma (DLBCL and multiple myeloma) have been opened and are enrolling patients.

1.3.2.1. Summary of Efficacy of Ibrutinib in CLL/SLL

In the Study PCYC-04753, 14/16 (87.5%) patients with CLL or SLL treated with ibrutinib met the protocol definition of evaluable for assessment of response. Twelve (12) of the 14 (86%) evaluable patients with CLL or SLL achieved a response by the International Workshop Chronic Lymphocytic Leukemia (IWCLL, Hallek 2008) criteria (hereafter referred to as IWCLL 2008 criteria) or National Cancer Institute (NCI) Working Group Criteria (for SLL). In patients with CLL (n = 11), the time to response was dependent on the time to resolution (< 50% of baseline circulating lymphocyte counts) of a treatment-related lymphocytosis that frequently occurs with the initiation of ibrutinib therapy. All responding patients with SLL (n = 5) met the standard Non-Hodgkin's lymphoma (NHL) response criteria by the Cycle 2 response assessment.

As of 25 October 2011, the PCYC-1102-CA study had enrolled 61 relapsed or refractory CLL/SLL patients who had previously received purine analog based therapy. These patients were given single-agent ibrutinib, which showed high activity as manifested by a high overall response rate (ORR) and an estimated 12-month progression-free survival (PFS) rate of 86%. Responses per IWCLL 2008 criteria improved with continued treatment; the ORR was 67% in patients treated with ibrutinib 420 mg/day at 12.6 months median follow-up. Responses were independent of high risk factors including disease resistant to purine analog based therapy, 17p del, age ≥70 years, and/or pretreatment cytopenias. The activity of ibrutinib was durable with an estimated 12-month PFS rate of 88% (Figure 1) in the 420 mg cohort. There were no differences in clinical activity (ORR or PFS) noted between the two dose levels (420 mg and 840 mg) (O'Brien 2011).

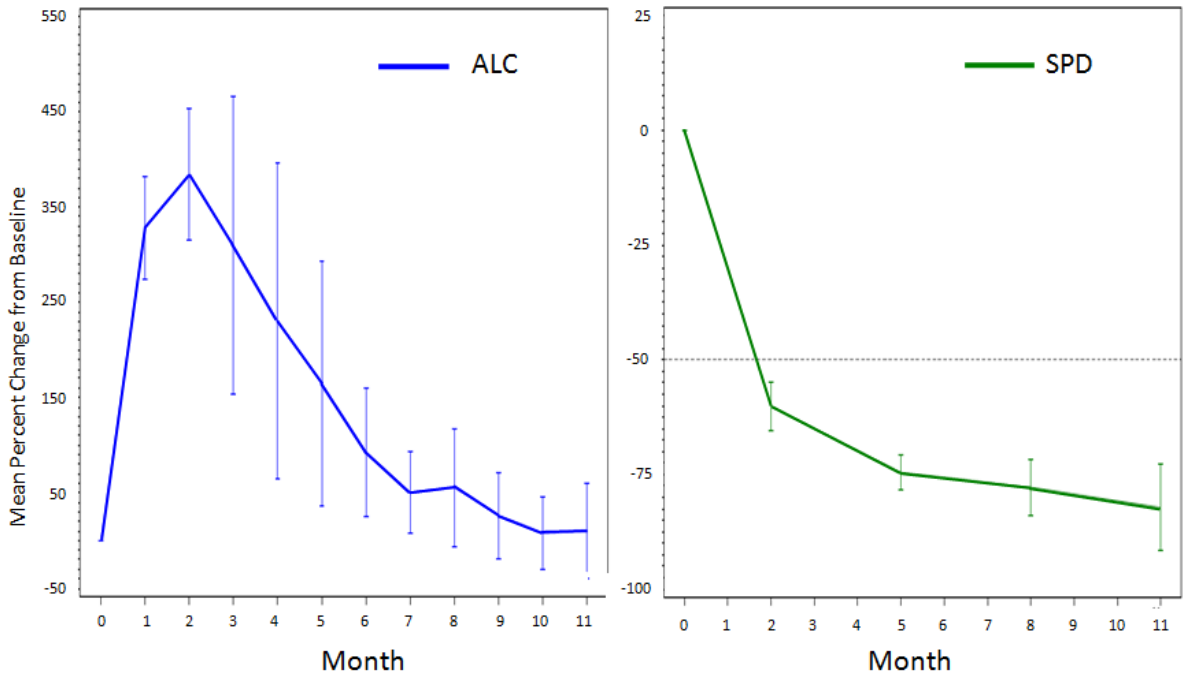
Figure 1: Progression-Free Survival Kaplan-Meier Curves, Study PCYC-1102-CA



Pharmacodynamic effect leading to characteristic pattern of response: Preclinical studies have revealed a vital and multifaceted role for BTK and the BCR signaling pathway in B-cell leukemogenesis and lymphomagenesis. These data suggest that the blockade of the BCR signaling pathway by ibrutinib in CLL results in three major effects: 1) direct induction of apoptosis and 2) inhibition of cell homing and migration to chemokines and with subsequent adhesion to cellular substrates, and 3) inhibition of proliferation (Herman 2011; Ponander 2012). Owing to the described mechanism of action of BTK inhibition, administration of ibrutinib to patients with lymphoproliferative diseases has been associated with mobilization of tumor cells from tissue to peripheral blood (Chang 2011b; Burger 2010; Pollyea 2009).

This effect begins in some cases within hours of the first administration and typically reaches peak magnitude within the first 3 months of treatment. Coincident with the ibrutinib treatment-related lymphocytosis is a rapid and substantial decrease in lymph node and/or spleen size often observed with or without an improvement in hematologic parameters and/or symptomatic improvement of disease-related symptoms. This effect was noted in CLL/SLL patients treated on both PCYC-04753 and PCYC-1102-CA (Figure 2).

Figure 2: Changes in Peripheral Blood Lymphocyte Counts and Burden of Lymphadenopathy in Patients with CLL/SLL, Study PCYC-1102-CA



ALC: Absolute lymphocyte count; SPD: Sum of products of lymph node dimension

This phenomenon is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of CLL cells from the lymph node to the peripheral blood compartment. This pattern of response had previously been noted with other agents known to inhibit BCR signaling (Friedberg 2008; Furman 2010). This treatment-related lymphocytosis resolves over a variable period of time (median 6 months) with the majority of patients meeting IWCLL 2008 criteria for response with continued ibrutinib treatment (O'Brien 2011). As such, an increase in the number of circulating lymphocytes in the peripheral blood in the absence of symptoms or other indicators of progressive disease has not been considered an indicator of progressive disease by the Investigators in clinical studies with ibrutinib. This is consistent with the recommendation of current National Comprehensive Cancer Network (NCCN) NHL 2012 guideline (Cheson 2012, Hallek 2012).

1.3.2.2. Summary of Clinical Safety of Ibrutinib

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

Pooled safety data from a total of 1318 subjects treated with ibrutinib monotherapy from 13 studies that have completed primary analysis or final analysis included in the CSR as of the 31 May 2016 cutoff date for the current ibrutinib IB update in B-cell malignancies are summarized below. Data for subjects in Study 1112 and in Study MCL3001 who crossed over from the comparator arm to ibrutinib treatment after progression are not included.

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

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

[a] Source is table 6 of ibrutinib IB; [b] Source is table 8 of ibrutinib IB; [c] Source is table 9 of ibrutinib IB.

1.3.3. Risks

1.3.3.1. Bleeding-related Events

There have been reports of hemorrhagic events in patients treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.6.1.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.6.3 for guidance on ibrutinib management with surgeries or procedures.

1.3.3.2. Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (> 400,000/μL) may confer increased risk. For subject and ibrutinib management guidance, refer to Section 6.2.5.

1.3.3.3. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 6.2.4).

1.3.3.4. Cytopenias

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

1.3.3.5. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 6.2.4).

1.3.3.6. Tumor Lysis Syndrome

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

1.3.3.7. Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥ 50% increase from baseline and an absolute count > 5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/SLL treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis (increase in the number of circulating lymphocytes eg, > 400,000/μL) is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy and typically resolves within a median of 8 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL. Lymphocytosis was not observed in subjects with Waldenström's macroglobulinemia treated with ibrutinib. For subject and ibrutinib management guidance, refer to Section 6.2.5.

1.3.3.8. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged, follow the protocol dose modification guidelines (see Section 6.2.4).

1.3.3.9. Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in subjects treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

1.3.3.10. Rash

Rashes have been commonly reported in subjects treated with either single agent ibrutinib or in combination with other chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.3.3.11. Non-melanoma Skin Cancer

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

1.3.3.12. Hypertension

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

2. STUDY RATIONALE

This randomized, multicenter, open-label, Phase 3 study is designed to evaluate whether treatment with ibrutinib as a monotherapy results in a clinically significant improvement in PFS

as compared to treatment with ofatumumab in patients with relapsed or refractory CLL or SLL who have failed at least one prior line of therapy and are not considered appropriate for treatment with purine analog based therapy.

The study design aims to confirm the efficacy findings of the ongoing Phase 1b/2 Study PCYC-1102-CA for treatment with ibrutinib administered orally once daily in the cohorts of patients with CLL/SLL who had failed previous treatment(s). This study will assess the efficacy outcomes between the two arms in relapsed/refractory patients, including those with a 17p del or who are refractory to purine analog based therapy. In addition, this study aims to confirm the safety and tolerability of ibrutinib in these patients as compared to an acceptable comparator, ofatumumab, in terms of hematologic and infectious toxicities.

2.1. Dose Selection Rationale for Ibrutinib

A once daily 420 mg dose of ibrutinib has been selected for this Phase 3 study. This dose and regimen were selected in consideration of PK, pharmacodynamics, efficacy, and safety data obtained from Studies PCYC-04753 and PCYC-1102-CA as detailed in Section 1.3. Ibrutinib has been administered safely at higher doses in CLL; however 420 mg once daily is considered an acceptable dose to achieve the desired biological effect, with no evidence of improved responses or improvement in PFS at doses above 420 mg/day (see Figure 1).

2.2. Selection of Ofatumumab as Comparator

Ofatumumab is a fully humanized type I anti-CD20 monoclonal antibody. *In vitro*, it mediates complement dependent cytotoxicity (CDC) against rituximab-resistant Raji cells and CLL cells with low expression of CD20. It appears to have greater potency in CDC than rituximab, as well as a slower off-rate and more stable CD20 binding (Teeling 2004). Additionally, it appears to bind a different epitope of CD20 than rituximab (Teeling 2006) and has demonstrated clinical activity that is independent of prior treatment with rituximab (Wierda 2011). A Phase 1/2 study of ofatumumab in relapsed/refractory CLL patients demonstrated that it is generally well-tolerated, even at high doses, and is active, with an ORR of approximately 50%. Infusion-related AEs are similar to those reported with rituximab and decrease following the first infusion (Coiffier 2008) of ofatumumab. Ofatumumab was evaluated in patients with fludarabine- and alemtuzumab-refractory (double refractory [DR]) and bulky fludarabine-refractory (BFR) CLL in a seminal study of 138 patients who have received treatment for CLL/SLL. Patients received 8 weekly infusions of ofatumumab followed by 4 monthly infusions over a 24-week period, receiving 300 mg as the first dose and 2000 mg for all doses thereafter (Wierda 2010). The ORR was 58% in the DR CLL group and 47% in the BFR CLL group with median PFS of 5.7 months and 5.9 months, and overall survival (OS) of 13.7 months and 15.4 months, for the two groups respectively. This data led to FDA (Food and Drug Administration) and EMA (European Medicines Agency) approval of ofatumumab in CLL in patients refractory to fludarabine and alemtuzumab. Currently NCCN NHL 2012 guidelines and European Society

for Medical Oncology (ESMO) guidelines support the use of ofatumumab in patients who have received treatment for CLL/SLL (NCCN 2012; Eichhorst 2011). The most common AEs for ofatumumab are infusion reactions, neutropenia, pneumonia, fevers, cough, and diarrhea. For more information on ofatumumab, please refer to the package insert.

3. STUDY OBJECTIVES

3.1. Primary Objective

To evaluate the efficacy of ibrutinib compared to ofatumumab based on independent review committee (IRC) assessment of progression-free survival (PFS) per International Workshop on Chronic Lymphocytic Leukemia Criteria (IWCLL, Hallek 2008) with incorporation of the clarification for treatment related lymphocytosis (Hallek 2012), hereafter referred to as IWCLL 2008 criteria in patients with relapsed or refractory CLL/SLL.

3.2. Secondary Objectives

To compare between the two treatment groups in terms of:

Efficacy

- To evaluate overall survival (OS)
- To evaluate IRC-assessed overall response rate (ORR) per IWCLL 2008 criteria
- To evaluate patient-reported outcome (PRO) by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACiT-Fatigue)
- To evaluate hematological improvement

Safety

To evaluate the safety and tolerability of ibrutinib compared to ofatumumab

3.3. Exploratory Objectives

To evaluate and compare between the two treatment arms in terms of:

- To evaluate Investigator-assessed PFS and ORR per IWCLL 2008 criteria
- To evaluate improvement and/or resolution of disease-related symptoms
- To evaluate PRO by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 (EORTC QLQ-C30) and EuroQoL Five-Dimension (EQ-5D-5L)
- To evaluate medical resource utilization (MRU)
- To determine the PK characteristics of ibrutinib in patients with CLL/SLL and to determine which, if any, covariates (eg, age, gender, body size, race) influence exposure to ibrutinib

- To investigate potential predictive biomarkers and mechanisms of resistance for the disease

4. STUDY DESIGN

This is a randomized, multicenter, open-label, Phase 3 study designed to evaluate the safety and efficacy of ibrutinib as compared to ofatumumab in patients with relapsed or refractory CLL/SLL who have failed at least one prior line of therapy and are not considered appropriate candidates for treatment or retreatment with purine analog based therapy.

Eligible patients will have been diagnosed with CLL/SLL and have relapsed or refractory disease following at least 1 line of prior systemic therapy for CLL/SLL.

A minimum of 350 patients will be randomized in a 1:1 ratio to receive either ofatumumab (Treatment Arm A) or ibrutinib (Treatment Arm B).

The site will enter eligibility data into an Interactive Web Response System (IWRS) prior to randomization.

Randomization will be used to minimize bias in the assignment of patients to treatment groups, to increase the likelihood that known and unknown patient attributes (eg, demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups. Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, patients will be randomized based on the following two stratification factors:

- Presence versus absence of disease refractory to purine analog and anti-CD20 containing chemoimmunotherapy regimen
- Presence versus absence of 17p del, as defined by the assay specification on pretreatment fluorescence in situ hybridization (FISH) or cytogenetics evaluation

Patient participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase.

The Screening Phase will be up to 28 days prior to first dose of study drug, during which the patient's eligibility and baseline characteristics will be determined.

The Treatment Phase will extend from randomization until study drug discontinuation. Patients randomized to ofatumumab will receive treatment for up to 6 months per the package insert. Patients randomized to ibrutinib will receive study drug daily until disease progression or unacceptable toxicity. Further information on dosing is provided in Section 6. Regularly scheduled disease assessments are required throughout the Treatment Phase.

The Follow-up Phase will be comprised of 2 phases; the Post-treatment Phase and a Post-disease Progression Phase. The Post-treatment Phase will extend from the discontinuation of treatment up until the patient has progressive disease or other criteria listed in Section 10.1. Response

evaluations will be continued every 12 weeks from the initial dose with study drug until 18 months and then every 24 weeks until disease progression.

The Post-disease Progression Phase will begin once a patient has progressive disease. In this phase, subsequent anticancer therapy with start date of therapy, IWCLL indication for treatment initiation, additional malignancy occurrence, and patient survival status will be recorded. The Post-disease Progression Phase will continue until death, lost to follow up, consent withdrawal, or study closure, whichever occurs first. It is important that survival status be assessed and that the date of death is documented for each patient randomized to treatment, regardless of whether or not the patient received treatment.

Assessment of response and progression will be conducted in accordance with the IWCLL 2008 criteria with the modification that treatment-related lymphocytosis in the absence of other signs or symptoms of disease progression will **not** be considered progressive disease (Section 8.1.5). The Investigator will evaluate sites of disease by radiological imaging (primary), physical examination or other procedures as necessary, review of hematology and serum chemistry results, and disease-related symptoms. The same methods of assessment used to assess disease at baseline should be used throughout the study. A central laboratory will perform all hematology and serum chemistry testing for the primary endpoint analysis. The primary efficacy analysis will be based on assessment from an IRC. As part of the IRC review, radiographic evaluations assessed by independent central radiologists and hematology results from a central laboratory will be provided. Detailed procedures will be described in a separate charter.

An independent Data Monitoring Committee (DMC) will be formed and constituted according to regulatory agency guidelines. Detailed information regarding the composition of the DMC and detailed DMC procedures will be provided in a separate charter. The DMC will review the safety data periodically and the interim analysis results and provide recommendations according to the charter.

One interim analysis using Lan-DeMets alpha spending function based on O'Brien-Fleming boundary for both superiority and futility (non-binding) is planned for the study. The interim analysis will be conducted after approximately 117 PFS events (progressive disease confirmed by the IRC or death, whichever occurs first) have occurred. The DMC will make recommendations based on efficacy boundary guidelines. If pre-specified boundaries are not met at the interim analysis, the final analysis of the study will occur after 176 PFS events have been observed.

Access to next-line ibrutinib for patients treated with ofatumumab may be provided following Medical Monitor approval as outlined in Section 7.3.4.

Pharmacyclics will continue to follow up the patients for at least 5 years after the last patient is enrolled, at which time a long-term extension study will be made available for active patients who choose to continue ibrutinib on a clinical protocol when access to commercial ibrutinib is not feasible.

5. SELECTION OF PATIENTS

5.1. Inclusion Criteria

Patients will be considered for inclusion in this study if they meet all of the following criteria:

1. Men and women ≥ 18 years of age
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
3. Diagnosis of CLL/SLL that meets published diagnostic criteria (Hallek 2008):
   a) monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing at least one B-cell marker (CD19, CD20, or CD23) and CD5
   b) Prolymphocytes may comprise no more than 55% of blood lymphocytes
   c) There is no evidence of cyclin D1 rearrangement or BCL-1 over expression
4. Active disease meeting at least 1 of the following IWCLL 2008 criteria for requiring treatment:
   a) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (Hgb < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/µL)
   b) Massive (ie, at least 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
   c) Massive nodes (ie, at least 10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy
   d) Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of less than 6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts (ALC) obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than 30 X 10^9/L (30,000/µL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded
   e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to standard therapy (see Appendix K)
   f) Constitutional symptoms documented in the patient's chart with supportive objective measures, as appropriate, defined as one or more of the following disease-related symptoms or signs:
      i) Unintentional weight loss ≥10% within the previous 6 months prior to Screening
      ii) Fevers higher than 100.5°F or 38.0°C for 2 or more weeks prior to Screening without evidence of infection
      iii) Night sweats for more than 1 month prior to Screening without evidence of infection

5. Must have received at least one prior therapy for CLL/SLL and not be appropriate for treatment or retreatment with purine analog based therapy, defined by at least one of the following criteria:
   a) Failure to respond (stable disease [SD] or disease progression on treatment), or a progression-free interval of less than 3 years from first dose of treatment with a purine analog based therapy and anti-CD20 containing chemoimmunotherapy regimen after at least two cycles
   b) Age ≥70 years, who had received >1 prior treatment including at least two cycles of an alkylating-agent based (or purine analog based) anti-CD20 antibody containing chemoimmunotherapy regimen or ≥2 prior lines of systemic therapy including chemotherapy, anti-CD20 or anti-CD52 monoclonal antibodies, or immunomodulatory therapy with lenalidomide or thalidomide
   c) Age ≥65 years with co-morbidities, who had received ≥1 prior treatment including at least two cycles of an alkylating-agent based (or purine analog based) anti-CD20 antibody containing chemoimmunotherapy regimen. Co-morbidities are defined by at least one of the following:
      i) Estimated creatinine clearance (ie, estimated Glomerular Filtration Rate, eGFR using) Cockcroft-Gault <70 mL/min
      ii) Platelet count <100,000/μL or hemoglobin <10 g/dL
      iii) History of clinically significant autoimmune cytopenia (controlled autoimmune hemolytic anemia or immune thrombocytopenia as defined in Appendix K)
      iv) Eastern Cooperative Oncology Group (ECOG) performance score = 1
   d) History of purine analog-associated autoimmune anemia or autoimmune thrombocytopenia temporally associated (within 4 weeks) of treatment with a purine analog
   e) The presence of 17p deletion by FISH
6. Measurable nodal disease by computed tomography (CT). Measurable nodal disease is defined as at least one lymph node > 1.5 cm in the longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended
7. Meet the following laboratory parameters:
   a) Absolute neutrophil count (ANC) ≥ 750 cells/μL (0.75×10^9/L) and independent of growth factor support 7 days prior to assessment
   b) Platelet count ≥ 30,000 cells/μL (30×10^9/L) without transfusion support 7 days prior to assessment. Patients with transfusion-dependent thrombocytopenia are excluded
   c) Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) < 2.5 x upper limit of normal (ULN)
   d) Total bilirubin ≤ 1.5 x ULN (unless due to Gilbert's syndrome or patients with autoimmune hemolytic anemia that is otherwise controlled)

e) Estimated creatinine clearance (ie, estimated Glomerular Filtration Rate, eGFR) using Cockcroft-Gault ≥ 30 mL/min

8. Able to provide written informed consent and can understand and comply with the requirements of the study
9. Able to receive all outpatient treatment, all laboratory monitoring, and all radiological evaluations at the institution that administers study drug for the entire study
10. Female patient of childbearing potential must have a negative serum or urine pregnancy test within 3 days of the first dose of study drug and agree to use dual methods of contraception during the study and for 1 month following the last dose with ibrutinib or 12 months following the last dose with ofatumumab. Post menopausal females (>45 years old and without menses for >1 year) and surgically sterilized females are exempt from this criterion
11. Male patient must use an effective barrier method of contraception during the study and for 3 months following the last dose if sexually active with a female of childbearing potential

5.2. Exclusion Criteria

Patients will be ineligible for this study if they meet any of the following criteria:

1. Known central nervous system (CNS) lymphoma or leukemia
2. Known prolymphocytic leukemia or history of or currently suspected Richter's transformation
3. Missing or incomplete documentation of cytogenetic and/or FISH results reflecting the presence or absence of 17p del and the percentage of cells with the deletion in patient records prior to randomization
4. Uncontrolled autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) defined as declining hemoglobin or platelet count secondary to autoimmune destruction within the screening period or requirement for high doses of steroids (>20 mg daily of prednisone daily or equivalent). See Appendix K.
5. Prior exposure to ofatumumab or to ibrutinib (PCI-32765) or randomization into an ibrutinib study
6. Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days prior to first dose of study drug
7. Corticosteroid use > 20 mg within 1 week prior to first dose of study drug, except as indicated for other medical conditions such as inhaled steroid for asthma, topical steroid use, or as premedication for administration of study drug or contrast. Patients requiring steroids at daily doses > 20 mg prednisone equivalent systemic exposure daily, or those who are administered steroids for leukemia control or white blood cell count lowering are excluded
8. Radio- or toxin-conjugated antibody therapy within 10 weeks prior to first dose of study drug

9. Prior autologous transplant within 6 months prior to first dose of study drug
10. Prior allogeneic stem cell transplant within 6 months prior to randomization or with any evidence of active graft versus host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug.
11. Major surgery within 4 weeks prior to first dose of study drug
12. History of prior malignancy, with the exception of the following:
    a) Malignancy treated with curative intent and with no evidence of active disease present for more than 3 years prior to Screening and felt to be at low risk for recurrence by treating physician
    b) Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer
    c) Adequately treated cervical carcinoma in situ without current evidence of disease
13. Currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (Appendix J), or history of myocardial infarction within 6 months prior to first dose with study drug
14. Unable to swallow capsules or disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption such as; malabsorption syndrome, resection of the small bowel, or poorly controlled inflammatory bowel disease affecting the small intestine
15. Uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) or ongoing intravenous anti-infective treatment
16. Known history of infection with human immunodeficiency virus (HIV)
17. Serologic status reflecting active hepatitis B or C infection. Patients with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction (PCR) result prior to enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
18. History of stroke or intracranial hemorrhage within 6 months prior to randomization.
19. Pregnant or lactating women
20. Current life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety or put the study at risk
21. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug
22. Requires treatment with a strong CYP3A4/5 inhibitor

6. TREATMENTS

Patients will be randomized 1:1 to either Treatment Arm A or B.

Treatment Arm A: Ofatumumab IV

Treatment is 12 IV doses over 24 weeks or until disease progression, unacceptable toxicity, or the patient meets any criteria specified in Section 10, whichever occurs first. Administration of ofatumumab will be in accordance with the manufacturer's package insert.

Treatment Arm B: Ibrutinib PO

Treatment is 420 mg (3 x 140-mg capsules) administered orally daily to continue until disease progression, unacceptable toxicity, or the patient meets any criteria specified in Section 10, whichever occurs first.

6.1. Ofatumumab

6.1.1. Dosage and Administration

6.1.1.1. Premedication

Patients should be premedicated 30 minutes to 2 hours prior to each dose of ofatumumab with 975-1000 mg acetaminophen/paracetamol; 10 mg Cetirizine orally or equivalent antihistamine, either IV or oral; and 100 mg IV prednisolone or equivalent corticosteroid.

Corticosteroid dose reduction:

- Do not reduce corticosteroid dose for ofatumumab infusions 1, 2, or 9.
- Corticosteroid doses may be reduced as follows:

  For Doses 3 through 8:

- If infusion-related reaction ≥ Grade 3 experienced, do not reduce corticosteroid dose for subsequent doses.
- If infusion-related reaction < Grade 3 experienced, may consider gradually reducing corticosteroid dose with subsequent doses.

  For Doses 10 through 12:

- If infusion-related reaction ≥ Grade 3 experienced with Dose 9, do not reduce corticosteroid dose for subsequent doses.
- If infusion-related reaction < Grade 3 experienced with Dose 9, may consider administering prednisolone 50 – 100 mg (or its equivalent) for subsequent doses.

Ofatumumab infusion premedication should be administered as outlined above and consistent with the package insert. It is recognized that some institutional variation to these procedures may exist, however for the purposes of this study; the package insert instructions must be followed. Routine infusion premedication with corticosteroid doses of > 100 mg IV prednisolone (or equivalent) is not permitted.

6.1.1.2. Dosage Regimen and Administration

Ofatumumab should be diluted in 0.9% Sodium Chloride Injection, USP and administered as an IV infusion. Do not administer the drug as an IV push or bolus.

The ofatumumab dosage and schedule is 12 doses administered as follows

Week 1: 300 mg initial dose

Weeks 2 through 8: 2,000 mg given weekly

Weeks 12, 16, 20 and 24: 2,000 mg every 4 weeks

An observation period following the end of infusion should occur as per the institution's standard practice. Refer to the Arzerra® package insert for additional administration instructions.

6.1.2. Dose Delay

Treatment with ofatumumab should be held for any unmanageable, potentially study drug-related toxicity that is Grade 3 or greater in severity. Additional information concerning dose delays can be found in Section 6.1.4.

Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the Medical Monitor.

Study drug may be held for a maximum of 28 days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the Medical Monitor.

6.1.3. Dose Interruption

Interrupt infusion for infusion-related reactions of any severity. For Grade 4 infusion-related reactions, do not resume the infusion. For Grade 1, 2, or 3 infusion-related reactions, if reaction resolves or remains ≤ Grade 2, resume infusion including increasing infusion rate consistent with the package insert according to the initial Grade of the infusion reaction:

- Grade 1 or 2: Infuse at one-half of the previous infusion rate
- Grade 3: Infuse at a rate of 12 mL/hour

6.1.4. Dose Discontinuation

The actions in Table 1 should be taken for the following toxicities:

- Grade 4 ANC (< 500/µL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2006] and use must be recorded in the case report form [CRF]).
- Grade 3 or 4 platelets (< 50,000/µL); or, in patients with baseline thrombocytopenia, a platelet decrease of 50-74% from baseline in presence of significant bleeding
- Grade 4 Platelets (< 25,000/µL); or, in patients with baseline thrombocytopenia, decrease of ≥ 75% from baseline or < 20,000/µL, whichever is higher

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

Table 1: Dose Discontinuation Actions for Ofatumumab

Occurrence	Action
1st–3rd	Hold ofatumumab until recovery to Grade ≤ 1 or baseline; may restart at original dose level
4th	Discontinue ofatumumab

In addition, discontinue ofatumumab if progressive multifocal leukoencephalopathy (PML) is suspected.

All patients will be screened for hepatitis B and those with evidence of chronic or active infection will be excluded from the protocol. However, if a patient develops viral hepatitis, they should be discontinued from ofatumumab treatment.

6.1.5. Dose Reduction

As dose reductions are not outlined in the package insert, dose reductions are not allowed for ofatumumab during this study.

6.1.6. Precautions and Adverse Effects

6.1.6.1. Warnings and Precautions

Infusion-Related Reactions: Premedication and infusion parameters, as outlined in the package insert should be used. Monitor patients closely during infusions and interrupt infusion if any reaction occurs.

Cytopenias: Monitor blood counts as outlined in the Schedule of Assessments (Appendix A).

6.1.6.2. Adverse Events

The most common serious adverse events (SAEs) with ofatumumab were infections (including pneumonia and sepsis), neutropenia, and pyrexia. Infections were the most common AEs leading to drug discontinuation. Additional common AEs (≥10%) with ofatumumab were cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections.

6.2. Ibrutinib

6.2.1. Dosage and Administration

Ibrutinib 420 mg (3 x 140-mg capsules) is to be administered orally once daily with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water.

Each dose of ibrutinib should be taken at approximately the same time each day. Patients should avoid consuming food and beverages containing grapefruit juice or Seville oranges for the duration of the study due to CYP3A4/5 inhibition. If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day.

Ibrutinib will be dispensed to patients in bottles. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 13.8) updated at each visit. Returned capsules must not be redispensed to anyone. Ibrutinib should not be dispensed to anyone other than a patient enrolled in the study and can only be dispensed in its original bottle.

6.2.2. Dose Delay

Treatment with ibrutinib should be held for any unmanageable, potentially study drug-related toxicity that is Grade 3 or higher in severity. Please see Section 6.6.1.4 for guidelines for management of ibrutinib in patients who require anticoagulant treatment.

Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the Medical Monitor.

Study drug may be held for a maximum of 28 consecutive days for toxicity. Study treatment should be discontinued in the event of a toxicity lasting >28 days, unless reviewed and approved by the Medical Monitor.

6.2.3. Overdose

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose.

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

Refer to Section 9.3 for further information regarding AE reporting.

6.2.4. Dose Reduction and Discontinuation

The actions in Table 2 should be taken for the following toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2006] and use must be recorded in CRF).
- Grade 3 or 4 platelets (< 50,000/μL); or, in patients with baseline thrombocytopenia, a platelet decrease of 50-74% from baseline in presence of significant bleeding
- Grade 4 Platelets (< 25,000/μL); or, in patients with baseline thrombocytopenia, decrease of ≥ 75% from baseline or < 20,000/μL, whichever is higher
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.6.1.4).

Table 2: Drug Discontinuation Actions for Ibrutinib

Occurrence	Action
1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level
2nd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (280 mg daily)
3rd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (140 mg daily)
4th	Discontinue ibrutinib

Dose changes must be recorded in the Dose Administration CRF.

6.2.5. Treatment-related Lymphocytosis

Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of ≥50% compared to baseline that occurs in the setting of improvement in at least one other disease-related parameter and is associated with agents known to inhibit BCR (see Section 8.1.5 for additional details) (Hallek 2012, NCCN 2012, Cheson 2012). Given the known mechanism of action of BCR-inhibiting agents including ibrutinib, treatment-related lymphocytosis is an expected and frequent pharmacodynamic phenomenon observed with initiation (or re-initiation) of ibrutinib. Ibrutinib associated treatment-related lymphocytosis generally occurs within the first weeks of therapy, peaks within the first few months, and resolves slowly. Asymptomatic treatment-related lymphocytosis should not be considered an AE and patients should remain on study treatment.

Specifically, upon initiation of treatment, a transient phase of increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count of 5,000/μL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/ refractory CLL/SLL and some patients (33%) with relapsed/refractory MCL treated with ibrutinib monotherapy. 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. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and resolves within a median of 7.1 weeks in the MCL and 18.7 weeks in the CLL patients.

A substantial increase in the number of circulating lymphocytes has been observed in a subset of patients. There have been isolated cases of leukostasis reported in patients treated with ibrutinib.

A high number of circulating malignant cells (≥400,000/μL) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and Medical Monitor should be contacted.

6.2.6. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child- Pugh class B or C) are excluded from study participation. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib/placebo is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix L).

6.2.7. Precautions and Adverse Events

The most common treatment-emergent adverse events were diarrhea, fatigue, nausea, cough and anemia. Additional common AEs such as peripheral edema, pyrexia, vomiting, constipation, upper respiratory tract infection, arthralgia, dyspnea, thrombocytopenia, decreased appetite, headache, muscle spasm, neutropenia, contusion, abdominal pain, dizziness, pneumonia, myalgia, and dyspepsia have been reported. In addition, Events of Special Interest are outlined in Section 9.3.4. For complete information on precautions refer to the IB.

6.3. Identification of Investigational Product(s)

6.3.1. Ibrutinib

Ibrutinib is provided as hard gelatin capsules containing 140 mg of ibrutinib. The capsules are packaged in opaque high-density polyethylene (HDPE) plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. The drug product is manufactured for Pharmacyclics LLC by a contract manufacturer. All formulation excipients are compendial and are commonly used in oral formulations.

The recommended storage condition for ibrutinib capsules is controlled room temperature. Formal International Conference on Harmonization (ICH) stability studies are ongoing to determine the shelf-life of the product. Please refer to the Pharmacy Binder and study drug label for more detailed information.

Refer to the IB for additional information regarding the drug product to be used in this study.

6.3.2. Ofatumumab

Ofatumumab, manufactured by GlaxoSmithKline, is provided in solution in single-use vials. Refer to the local ofatumumab package insert for details.

6.4. Treatment Compliance

Patient compliance with ibrutinib will be assessed by the site pharmacist or designee at each visit using direct questioning, examination of patient diaries, and capsule counts. Ofatumumab compliance will be performed by the site pharmacist or designee as patients will not be taking the study drug home.

Compliance will be verified by the Sponsor or designee and will be recorded in the study Pharmacy Binder. The pharmacist or designee will:

- Maintain records of product delivery, inventory, return, and destruction
- Maintain temperature monitoring
- Maintain up-to-date accountability of the study drug in the study drug accountability log (or equivalent)
- Document the use of study product by each patient
- Return or destroy unused study product as per Sponsor's instructions

6.5. Randomization and Blinding

A minimum of 350 patients will be randomized in a 1:1 ratio to each of the 2 treatment arms in this study. Randomization will be used to minimize bias in the assignment of patients to the 2 treatment arms. Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, randomization will be

stratified using the following two factors: 1) presence versus absence of refractory disease to purine analog and anti-CD20 containing chemoimmunotherapy regimen, and 2) presence versus absence of 17p del.

This is an open-label study; neither patients nor Investigators will be blinded to treatment.

The primary efficacy evaluation will be performed by an IRC, which will be blinded to study treatment information and lymphocyte count.

6.6. Concomitant Therapy

6.6.1. Concomitant Medications to be Used With Caution

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted; this includes pre-medication for ofatumumab infusion as per the ofatumumab package insert. Use of neutrophil growth factors (filgrastim and pegfilgrastim) is permitted per the American Society of Clinical Oncology (ASCO) guidelines (Smith 2006).

For patients considered at risk for tumor lysis syndrome (TLS):

Patients with more than one of the following factors are considered to be at increased risk of TLS and should be considered for hydration and treatment with an uric acid lowering agent (xanthine oxidase inhibitor allopurinol or Uloric [febuxostat] +/- rasburicase per the drug products package insert) prior to treatment with study drug, as well as for frequent monitoring of tumor lysis associated signs and symptoms.

- Serum creatinine ≥ 1.5x ULN
- WBC ≥ 50,000/mm^3
- Uric acid > ULN

6.6.1.1. Guideline for Use of CYP Inhibiting/Inducing Drugs

Ibrutinib is metabolized primarily by CYP3A4. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and $AUC_{0\text{-}last}$, of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, consider reducing the ibrutinib to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 mg for

the duration of the inhibitor use. Monitor subject for toxicity and follow dose modification guidance as needed. For subjects who are already on a moderate CYP3A inhibitor concomitantly with ibrutinib without significant toxicity the investigator may consider the overall risk-benefit to determine if a dose reduction of ibrutinib is appropriate. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 6.2.1). No dose adjustment is required in combination with weak CYP3A inhibitors.

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

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

6.6.1.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 µg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. Currently, no clinical data is available; therefore, co-administration of narrow therapeutic index P-gp substrates (eg, digoxin) with ibrutinib may increase the substrate's blood concentration and should be used with caution and subjects should be monitored closely for toxicity.

6.6.1.3. Concomitant Use of QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with electrocardiograms and electrolytes should be considered.

6.6.1.4. Concomitant Use of Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Ibrutinib should be used with caution in patients requiring other anticoagulants or medications that inhibit platelet function. Supplements such as fish oil and vitamin E preparations should be avoided. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries see Section 6.6.3.

Patients requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the patient

is clinically stable and has no signs of bleeding. Patients should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.6.2. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone >20 mg/day), experimental therapy, or radiotherapy are prohibited. Localized, hormonal, or bone sparing treatment for non-B cell malignancies may be considered with approval of the medical monitor. Steroids used to premedicate or manage ofatumumab infusion-related reactions or contrast allergies are permitted. In addition, short courses (<14 days) of treatment for non-cancer related medical reasons (treatment for autoimmune cytopenias are permitted) at doses not to exceed 100 mg/day of prednisone or equivalent are permitted. Routine infusion premedication with corticosteroid doses of >100 mg IV prednisolone (or equivalent) is not permitted. Red blood cell growth factors (eg, erythropoietin), platelet growth factors (eg, thrombopoietin) and sargramostim are also prohibited for the first six months of study treatment. However, initiation of red blood cell growth factors (eg, erythropoietin), platelet growth factors (eg, thrombopoietin) and/or sargramostim can be considered after 6 months on study based on the indication outlined in the respective package inserts.

6.6.3. Guidelines for Ibrutinib Management with Surgeries or Procedures

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

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7. EFFICACY AND SAFETY PROCEDURES

The Schedule of Assessments is provided in Appendix A. Descriptions of the scheduled evaluations are outlined below.

Before study entry, throughout the study, and at the follow-up evaluations, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and efficacy assessments. Clinical evaluations and laboratory assessments may be repeated more frequently if clinically indicated.

7.1. Description of Procedures

7.1.1. Informed Consent

The patient must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC)-approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Patients must also grant permission to use protected health information per Health Insurance Portability and Accountability Act (HIPAA). In addition, patients must sign all approved ICF amendments per the site IRB/REC/IEC's guidelines during the course of the study.

7.1.2. Confirmation of Eligibility

Perform all necessary procedures and evaluations to document that the patient meets each eligibility criterion (Section 5). Please refer to the study manual for a more detailed description of the enrollment procedures. Blood samples for hematology, coagulation, and serum chemistry collected at Screening will be evaluated by a central laboratory to confirm eligibility. If central labs submitted during the screening period are unable to be resulted (eg, specimen clotted or hemolysis) to support eligibility, the Medical Monitor may review local labs and approve the patient for randomization based on these lab values on a case by case basis provided another sample is redrawn and submitted prior to treatment.

7.1.3. Medical History

Collect and record the patient's complete history including concurrent medical signs and symptoms. Disease history, including the date of initial diagnosis, Rai and Binet staging (Appendix I) within 28 days of first dose with study drug, documentation of refractory disease, prior anticancer treatments with best responses and progression free interval to these treatments, and history of autoimmune CLL complications and their treatment will also be recorded based upon available documents and patient history.

7.1.4. Adverse Events

The accepted regulatory definition for an AE is provided in Section 9.2. All medical occurrences that meet the AE definition must be recorded from the time the ICF is signed until 30 days after the last dose of study drug. Laboratory abnormalities designated clinically significant by the

Investigator will also be recorded as AEs. Additional important requirements for AE and SAE reporting are explained in Section 9.3.

7.1.5. Physical Examination, Height and Weight

Physical examinations should include height (Screening only) and weight, examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, and lymphatic system. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes and measurement of spleen and liver sizes by centimeters below the costal margin on the respective side. Only physicians, physician assistant, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic exams for a given patient.

7.1.6. Eye-related Symptoms Assessment

The patients will be asked about the following eye-related symptoms at Screening and throughout the study: dry eye, watering eye/abnormal discharge, eye pain, blurred vision/double vision, decreased visual acuity, photophobia/sensitivity to light, floaters, flashing lights, and eye irritation.

If there are any symptoms of severity ≥ Grade 2 at Screening, an ophthalmologic exam must be completed prior to dosing with study drug. If, during the study, any symptom worsens to severity ≥ Grade 2 or a symptom that was Grade 2 or higher at baseline worsens, an ophthalmologic exam must be performed.

7.1.7. Disease-related Symptoms

Disease-related symptoms including fatigue, night sweats, fever, weight loss, anorexia, and symptoms of splenomegaly (abdominal pain/discomfort) will be assessed and recorded in the patient records.

7.1.8. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature.

7.1.9. Electrocardiogram (ECG)

Patients should have a 12-lead ECG done at Screening. Abnormalities should be included in the medical history, as appropriate.

ECGs should be performed at the investigator's discretion, particularly in patients with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea.

7.1.10. ECOG Performance Status

The ECOG performance index is provided in Appendix B.

7.1.11. Cumulative Illness Rating Scale (CIRS)

CIRS is an indicator of illness severity and comorbidity in older patients (Extermann 1998).

CIRS scoring is to be performed by a licensed provider (eg, physician, physician assistant, or nurse) for all patients 65 years and older in the setting of a pretreatment history and physical (refer to Appendix H for details).

7.1.12. Prior and Concomitant Medications

Document all medications from 14 days before the start of study drug administration through 30 days after the last dose of study drug.

After a patient discontinues study treatment, receipt of all subsequent anticancer therapies will be collected until patient death.

7.1.13. Patient-reported Outcomes (PRO)

Three PRO instruments, including the EORTC QLQ-C30 (Appendix E), EQ-5D-5L (Appendix F), and FACiT-fatigue (Appendix G), will be administered in this study. These questionnaires are to be completed by the patient prior to any other study procedures at required visits.

7.1.13.1. EORTC QLQ-C30

The EORTC QLQ-C30 includes 30 separate questions (items) resulting in 5 functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), 1 Global Health Status scale, 3 symptom scales (Fatigue, Nausea and Vomiting, and Pain), and 6 single items (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties) (Fayers 2001). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients in general, and specifically in NHL patients. It is a reliable and valid measure of PRO in cancer patients and takes about 11 minutes to administer.

7.1.13.2. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (The Euro Qol Group 1990). The EQ-5D-5L is a 5-item questionnaire and a “thermometer” visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questionnaires are categorical and should not be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a

single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The United Kingdom weights will be used to generate patient utilities from the 5 dimensions of the EQ-5D-5L in this study.

7.1.13.3. FACiT-Fatigue

The FACiT-Fatigue questionnaire is an instrument for use as a measure of fatigue-related quality of life in patients with cancer and other chronic diseases (http://www.facit.org). The 13-item FACiT-Fatigue Scale measures each item on a 5-point Likert scale. The FACiT-Fatigue Scale has been validated in the general population (Cella 2002) as well as in patients with cancer or rheumatoid arthritis.

7.1.14. Pregnancy Test

Pregnancy tests (urine or serum) are required at Screening only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible. This test may be performed more frequently if required by local regulatory authorities.

7.1.15. Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody and will be evaluated by central laboratory. Hepatitis B surface antigen must be confirmed negative prior to enrollment. If Hepatitis B core antibody is positive, then Hepatitis B PCR to quantitate Hepatitis B DNA must be performed. DNA PCR needs to be confirmed negative (<29 U) prior to randomization in patients who are Hepatitis B core antibody positive. Patients who are hepatitis C PCR positive will be excluded.

7.1.16. Hematology

Hematology will be evaluated by a central laboratory and will include a complete blood count (CBC) with white blood cell differential. Any missing central lab blood samples should be redrawn as soon as possible. In the event that the missing central lab sample is unrecoverable, local lab results will be collected, if available, and entered in the clinical database for response or progression confirmation.

7.1.17. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening using a central laboratory. Any missing central lab blood samples should be redrawn as soon as possible.

7.1.18. Serum Chemistry

Serum chemistry will be evaluated by a central laboratory and will include albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), calcium, creatinine, glucose, lactate dehydrogenase (LDH), phosphate, potassium, sodium, total bilirubin, and uric acid. Any missing central lab blood samples should be redrawn as soon as possible.

7.1.19. Serum Immunoglobulin and β_2-microglobulin

Sample(s) will be sent to a central laboratory for quantitative immunoglobulin (IgG, IgM, IgA) levels, and serum β_2-microglobulin.

7.1.20. Sparse Pharmacokinetics (PK) Sample Collection

Sparse PK samples will be collected in patients randomized to ibrutinib. Samples will be collected from at least 100 patients. Five (5) blood samples will be collected per patient on the Week 1 Visit**.**

1. Pre-dose
2. 1 hour (window: 45–75 minutes)
3. 2 hours (window: 1.5–2.5 hours)
4. 4 hours (window: 3.5–4.5 hours)
5. 6 hours (window: 5–8 hours)

Patients will also undergo sampling at the **Week 4* visit.** These patients will be sampled at:

1. Pre-dose
2. 1 hour (window: 45–75 minutes)
3. 2 hours (window: 1.5–2.5 hours)
4. 4 hours (window: 3.5–4.5 hours)

On the day of the sampling visit, the patient will not take a dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The time of the PK sample and the time of the study drug dose will be recorded in the CRF.

*Note: If patient is unable to complete PK assessments at the Week 4 visit, it is acceptable to complete these assessments at the Week 8 visit.

7.1.21. Pharmacokinetics Sample Collection for Patients Treated with Concomitant CYP3A4/5 Inhibitors on Ibrutinib Treatment

For patients who must take strong or moderate CYP3A4/5 inhibitors while on treatment with ibrutinib, additional PK collections for evaluation of ibrutinib exposure may be requested at the following scheduled visit after concomitant CYP3A4/5 inhibitor has started and still in use. PK samples will be collected at:

1. Pre-dose
2. 1 hour (window: 45–75 minutes)
3. 2 hours (window: 1.5–2.5 hours)

On the day of the sampling visit, the patient will not take the dose of ibrutinib before arrival at the clinic. Study drug intake will be observed by clinic staff. The time of the PK sample and the time of the study drug dose will be recorded.

7.1.22. Bone Marrow Aspirate and Biopsy

For Eligibility

A unilateral bone marrow aspirate or biopsy must be obtained at Screening or up to 90 days prior to randomization. Patients who have a bone marrow aspirate or biopsy result since completion of their last therapy for CLL may use those bone marrow results provided the biopsy or aspirate was done <90 days prior to randomization.

For Response Evaluation

If the patient's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved in all response parameters, a bone marrow aspirate and biopsy must be obtained to confirm the CR and to evaluate minimal residual disease (MRD) by flow cytometry. In the event a marrow aspirate was not successfully submitted for MRD, a peripheral blood sample should be submitted. In cases where cytopenic progression is suspected, a bone marrow aspirate or biopsy should be performed to distinguish autoimmune and drug-related cytopenias.

7.1.23. Cytogenetic CLL FISH Panel

Cytogenetic profiles will use the standard CLL FISH probes to detect abnormalities in chromosomes 13q, 12, 11q, and 17p. Within 90 days prior to randomization, a peripheral blood sample or bone marrow sample (aspirate or biopsy) must be tested for FISH analysis for stratification purpose. For patients without lymphocytosis FISH should be performed on the bone marrow sample. A previous FISH and/or cytogenetic result demonstrating the presence of 17p del as per the assay specification will be considered adequate for stratification provided appropriate documentation is available. Results must be documented in the patient chart prior to randomization for the purposes of stratification. At Screening, peripheral blood will be collected for confirmation of FISH result. Screening peripheral blood (required) and marrow samples (where available) will be sent to a central vendor to be tested for 17p del, 13q-, +12, 11q-, to assist with the validation of the Abbott probe kit for use as prognostic marker.

7.1.24. Determination of T/B/NK Counts

In order to monitor the effects of ibrutinib on the immune cells in patients, specifically on the normal B cells, T cells and NK cells, whole blood samples will be analyzed for absolute T/B/NK

counts (CD3, CD19, CD4, CD8, CD16/56) using a standard cell marker panel. This assay will be performed at the central lab on the same blood sample collected for standard hematology.

7.1.25. Flow Cytometry-based Immunophenotype Assays

To determine the temporal effect of study drugs on the phenotype of malignant cells in patients, blood samples will be collected and analyzed centrally. Samples taken in the first 6 months will be more frequent in order to capture the treatment-effect of lymphocytosis. Samples will also be collected at a suspected CR and at disease progression or discontinuation of treatment. From these samples, peripheral blood mononuclear cells (PBMC) will be separated, collected and frozen as viable cells. The cell pellets will be analyzed at a future date by flow cytometry, for expression of cell surface markers including CD3, CD19, CD45, CD5, Igλ/κ+, CXCR4 and CD38. These samples will also be stained intracellularly for Ki67, pBtk, pSyk, pPLCγ, pErk and pAkt to monitor changes taking place within the tumor cells.

7.1.26. Genetic and Molecular Prognostic Markers

A blood sample will be collected and analyzed centrally to study the pretreatment prognostic factors. These prognostic factors have previously been associated with disease outcome in CLL patients.

IgVH and p53 Mutational Status

One sample will be collected to study leukemia cell immunoglobulin heavy-chain variable (IgVH) and p53 mutational status.

CD38 and ZAP-70 Leukemia Cell Expression

One sample will be collected to study the leukemia cell expression of CD38 and ZAP-70.

7.1.27. Exploratory Investigations of Predictive Biomarkers and Mechanism of Treatment Resistance

Additional blood samples will be collected and assessed or maintained centrally to evaluate potential biomarkers related to response to therapy and/or to investigate potential mechanisms of treatment resistance. These samples may be later characterized by technologies such as gene expression profiling, mutational analysis by sequencing, secreted protein analysis, and intracellular signaling pathway analysis. Inhibition of BTK and other related kinases may also be explored in these cells. It is expected that these efforts may identify genes and pathways associated with primary or later development of resistance to ibrutinib by comparison of patients with variable outcomes which could potentially generate biomarkers that could assist with future development of this compound.

7.1.28. Computed Tomography (CT) Scans

Radiological imaging by CT with contrast is required and must include the pelvis, abdomen, chest, and neck. Patients who are intolerant to IV CT contrast agents will have CT scans performed with oral contrast. When possible, all patients should have radiographic tumor measurements performed at the participating study center or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment. The same imaging equipment should be utilized for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given patient throughout the study as much as possible.

Magnetic resonance imaging (MRI) may be used to evaluate nontarget lesions that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations). If MRI is required for any other reason, this must be discussed with the study Medical Monitor first.

CT scans will be performed until disease progression regardless of whether or not the patient remains on treatment. In the event disease progression is suspected due to physical examination or laboratory test, a CT scan must be performed to confirm disease progression.

There must be radiographically measurable disease at Screening (at least one lymph node > 1.5 cm in the longest diameter) as outlined in Section 8.1.4. If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion.

Up to 6 measurable lymph nodes (target lesions > 1.5 cm in the longest diameter), clearly measurable in 2 perpendicular dimensions, will be followed as target lesions for each patient. Measurable sites of disease should be chosen such that they are representative of the patient's disease. In addition, selection of target lesions should be from as disparate regions of the body as possible when these areas are significantly involved. If additional lesions are present but are not included in the target lesion assessment, they can be added as non-target lesions followed throughout the study.

The cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at Screening and all subsequent response evaluations.

A central imaging service will be utilized to provide independent radiological assessments for the purposes of the primary endpoint. These measurements will not be reported back to the site.

7.1.29. Medical Resources Utilization (MRU)

Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected for each treatment arm.

7.1.30. Routine Clinical Assessments

Routine clinical assessments include physical exams, recording of symptoms, and hematological evaluations to evaluate for both AEs and for disease progression at times when the CT scan is

not obtained. If a patient shows signs of progression, the patient may continue treatment until progression is confirmed. The Investigator should report any suspected disease progression to the Sponsor or designee via the electronic data capturing (EDC) system within 24 hours of discovery. Patients should continue to be followed and adhere to study-related procedures until progression has been confirmed regardless of the administration of subsequent anticancer therapy. New anticancer therapy may be withheld if clinically appropriate in the absence of confirmed progressive disease. In addition, lab assessments for disease progression will need to be confirmed by the central lab.

7.1.31. Overall Response Evaluations

Overall response assessments will include evaluation of physical exams, recording of symptoms, hematological evaluations, and radiographic evaluations per the schedule of assessments (see Appendix A and Appendix M). Patients who have signs and symptoms of progression outside of the scheduled assessment, should be evaluated by the investigator with a physical exam and a CBC with differential to determine if disease progression is present. Patients may continue study treatment until progression is confirmed by a serial exam at least 2 weeks later. In addition, when clinically appropriate, based on investigator perceived risk benefit assessment, a patient may continue treatment until progression is confirmed, unless considered medically contraindicated. New anticancer therapy may be withheld if clinically appropriate in the absence of confirmed progressive disease. The blood samples for response or disease progression determination will need to be confirmed by a central laboratory.

For response assessments occurring without a CT scan, the investigator should evaluate response on available clinical data, including physical examinations and laboratory results. For patients who appear to be CR by all other parameters, a CT scan and evaluation of MRD status are required to confirm CR.

Following the DMC review of interim efficacy analysis data, procedures surrounding expedited reporting of progressive disease are not required and IRC review may no longer occur.

7.1.32. Survival

After progression, patients will be contacted to assess survival status approximately every 12 weeks until death, withdrawal by patient, lost to follow-up, or study terminated by Sponsor, whichever comes first. At the time of the interim analysis and at study closure, a survival sweep will be conducted. All patients who are on study and not known to have died prior to the survival sweep will be contacted at that time.

7.1.33. Subsequent Anticancer Therapies

After study drug treatment is complete, the following information on subsequent anticancer therapies will be collected approximately every 12 weeks until death, withdrawal by patient, lost to follow-up, or study terminated by Sponsor, whichever comes first:

- Receipt of all subsequent anticancer therapies
- IWCLL indication for initiation of subsequent anticancer therapy
- Response to all subsequent anticancer therapies

7.2. Drug Concentration Measurements

7.2.1. Sample Collection and Analysis

Sparse PK samples will be collected from at least 100 patients on the ibrutinib arm. Refer to the laboratory binder for instructions on collecting and processing these samples.

Plasma samples will be analyzed by a validated and specific LC-MS/MS method for the determination of ibrutinib and PCI-45227, a metabolite of ibrutinib, in human plasma. Exploratory analyses may be performed for other potential metabolites of ibrutinib in plasma.

7.2.2. Pharmacokinetic Assessment

Plasma concentrations, dosing history, demographic data, and other covariates will be assembled into a dataset suitable for a population PK analysis. The analysis will be performed using mixed-effects methods.

Based on previous PK studies for ibrutinib, it is likely that the structural model will include two systemic compartments and first-order absorption and will be linear with respect to dose and stationary with respect to time. Parameters of the PK model will be apparent clearance, apparent distribution clearance, apparent distribution volumes (central and peripheral), absorption rate, and absorption lag. Absorption, distribution, and elimination half-lives and steady-state AUC will be calculated from these parameters.

If the assumptions of linearity and stationarity are flawed, other models will be evaluated. After determination of the structural model, covariates will be evaluated for inclusion into the model using forward addition. The final model will be evaluated using one or more of the following methods: visual predictive check, likelihood profiles, or bootstrap analysis.

Similar analyses will be performed for PCI-45227.

For patients who received CYP3A4/5 inhibitors, as data permitted, a descriptive comparison of ibrutinib and PCI-45227 plasma concentrations after ibrutinib administration alone and in combination with CYP3A4/5 inhibitors will be explored.

Pharmacokinetic relationships to pharmacodynamic measures of efficacy or toxicity will also be explored.

7.3. Assessments by Visit

7.3.1. Screening Phase

The procedures below will be performed for potential patients within 28 days of Week 1 Visit:

- Informed consent
- Review of eligibility criteria
- PRO assessments
- Adverse events
- Medical history
- Physical examination
- Eye-related symptoms
- Vital signs
- 12-lead ECG
- ECOG performance status
- Prior medications (including chemotherapy, radiation, over-the-counter drugs, vitamins and herbs)
- Pregnancy test (for women of childbearing potential only)
- Hepatitis serologies
- Hematology
- Coagulation parameters
- Serum chemistry
- Genetic and molecular prognostic factors
- Radiologic exam by CT (within 6 weeks of randomization)
- Bone marrow biopsy and aspirate (within 90 days of randomization)
- Cytogenetic, CLL FISH panel (within 90 days of randomization, see Section 7.1.23)

7.3.2. Treatment Phase

Following completion of the Screening Visit and once eligibility has been confirmed, patients will be randomized to either ofatumumab or ibrutinib via an automatic IWRS or alternative system provided by the Sponsor. Randomization should occur as close to the time of the expected first dose as possible but no later than 3 business days prior to expected first dose with study drug.

Study drug treatment should be continued until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 10.1. Local labs may be used to guide all dosing-related decisions and should be followed up with central labs. In the event of clinically

suspected disease progression, the patient may continue to receive study medication until disease progression is confirmed at the discretion of the Investigator.

Refer to the Schedule of Assessments (Appendix A) for a complete list of procedures to be performed at each scheduled study visit.

7.3.2.1. Pre-Dose Week 1 Visit

The following procedures will be performed prior to dosing (within 3 days) of the Week 1 Visit. Please note, Week 1 Visit procedures done at Screening will not need to be repeated if done within 3 days of first dose with study drug.

- Confirmation of eligibility
- Update medical history
- Cumulative Illness Rating Scale (CIRS) (for patients ≥65 years of age only)
- Adverse events
- Physical examination
- Disease-related symptoms (no longer required per Amendment 5)
- Vital signs
- ECOG performance status
- Concomitant medications
- Hematology
- Serum chemistry
- Serum immunoglobulins and β2-microglobulin
- Pre-dose PK sample (ibrutinib arm only)
- T/B/NK cells
- Flow cytometry-based immunophenotype assays
- Predictive biomarkers and mechanisms of resistance

7.3.2.2. Dose Week 1 Visit

- Administration of ofatumumab or ibrutinib

7.3.2.3. Post-Dose Week 1 Visit

- Adverse events
- Concomitant medications
- Sparse PK sample at 1, 2, 4, and 6 hours (ibrutinib arm only)
- MRU (no longer required per Amendment 5)

7.3.2.4. Week 2, 3, 5, 6, and 7 Visits

The following procedures will be performed, however, patients on the ibrutinib arm may have their blood drawn for the central lab submission at the site lab and do not need to return to clinic:

- Administration of ofatumumab in clinic (ofatumumab arm only)
- Hematology
- Flow cytometry-based immunophenotype assays (Weeks 3 & 5 only)
- Predictive biomarkers and mechanisms of resistance (Weeks 3 & 5 only)
- Adverse events (by telephone contact for ibrutinib arm patients if not seen in the clinic)
- Concomitant medications (by telephone contact for ibrutinib arm patients if not seen in the clinic)
- MRU (by telephone contact for ibrutinib arm patients if not seen in the clinic) (no longer required per Amendment 5)

7.3.2.5. Week 4-24 Visits, every 4 weeks

The following procedures will be performed:

- Administration of ofatumumab or ibrutinib
- Physical examination
- Eye-related symptoms (Weeks 12 and 24)
- Disease-related symptoms (no longer required per Amendment 5)
- Vital signs
- ECOG performance status
- PRO assessments
- Concomitant medications
- Adverse events
- Hematology
- Serum chemistry
- Sparse PK sample (ibrutinib arm - Week 4 only)
- T/B/NK cells (Weeks 12 and 24)
- Flow cytometry-based immunophenotype assays (Beginning at Week 8)
- Serum immunoglobulins and β2-microglobulin (Weeks 12 and 24)
- MRU (no longer required per Amendment 5)

7.3.2.6. Weeks 36 until Discontinuation of Treatment, every 12 weeks

The following procedures will be performed:

- Physical examination
- Eye-related symptoms (every 12 weeks until 18 months, then once every 24 weeks)
- Disease-related symptoms (no longer required per Amendment 5)
- Vital signs
- ECOG performance status
- PRO assessments
- Concomitant medications
- Adverse events
- Hematology
- Serum chemistry
- Serum immunoglobulins and β_2-microglobulin
- T/B/NK cells
- Flow cytometry-based immunophenotype assays
- Predictive biomarkers and mechanisms of resistance
- MRU (no longer required per Amendment 5)

7.3.2.7. Response Evaluations, every 12 weeks from first dose until progression

The following procedures will be performed in conjunction with standard visits every 12 weeks and then every 24 weeks after 18 months until the patient exhibits disease progression:

- Radiologic exam by CT, only required every 24 weeks after 12 months, and annually after 36 months
- Overall response assessment
- Bone marrow biopsy (when appropriate to confirm CR or evaluate cytopenia)

7.3.2.8. End-of-Treatment Visit

The following will be performed 30 (± 3) days after the discontinuation of treatment with study drug:

- Physical examination
- Vital signs
- ECOG performance status
- Eye-related symptoms

- Disease-related symptoms (no longer required per Amendment 5)
- PRO assessments
- Concomitant medications
- Adverse events
- MRU (no longer required per Amendment 5)
- Hematology
- Serum chemistry
- Flow cytometry-based immunophenotype assays
- Predictive biomarkers and mechanisms of resistance

7.3.3. Follow-up Phase

7.3.3.1. Post-treatment Phase

After discontinuation of treatment, the following assessments will be performed every 12 weeks (±7 days) until disease progression or study closure, whichever is earlier:

- Subsequent anticancer therapies
- Physical examination and ECOG performance status
- Disease-related symptoms (no longer required per Amendment 5)
- MRU (no longer required per Amendment 5)
- PRO assessments
- Hematology
- Serum immunoglobulins and β_2-microglobulin
- T/B/NK cells
- Flow cytometry-based immunophenotype assays
- Predictive biomarkers and mechanisms of resistance

Prior to disease progression, response assessment (including CT, CBC and PE) need to be continued on a calendar schedule even if the patient receives subsequent anticancer therapy.

7.3.3.2. Post-disease Progression Phase

Once patient progresses, the following assessments will be assessed every 12 weeks until death, withdrawal by patient, lost to follow-up, or study terminated by Sponsor, whichever comes first.

- Subsequent anticancer therapies
- MRU (no longer required per Amendment 5)
- Survival status

- Occurrence of any additional malignancy
- Occurrence of transformation to a more aggressive histology (Richter's transformation)

7.3.4. Treatment with Ibrutinib for Patients on Control Arm

On 03 January 2014, the DMC determined that the primary endpoint of the study had been met and the analysis be considered final. Patients randomized to ofatumumab who meet the criteria outlined in Section 7.3.4.1, per the investigator's discretion, can receive next-line therapy with ibrutinib and will follow the schedule in Appendix M. Treatment with ibruntib can be continued until disease progression as determined by the investigator, or until they meet the criteria for withdrawal in Section 10. Patients must meet all of the criteria for next-line therapy with ibrutinib listed in Section 7.3.4.1. With Medical Monitor approval, local labs can be used to determine appropriateness for next-line ibrutinib.

7.3.4.1. Criteria for Next-line Ibrutinib Therapy

1. Medical Monitor approval
2. ECOG Performance Status of ≤3 (Appendix B)
3. Platelet count ≥25,000/µL
4. No uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment)
5. No currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (Appendix J), or history of myocardial infarction within 6 months prior to first dose with study drug
6. Recovered from the acute toxicities due to prior chemotherapy, radiotherapy, investigational drugs, or experimental treatments (non-hematologic toxicities have resolved to a NCI CTCAE [version 4.0] Grade of ≤2)
7. No known Richter's transformation
8. Does not require or receive anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon)
9. Female patient of childbearing potential must have a negative serum or urine pregnancy test within 3 days of the first dose of study drug and agree to use highly effective method of contraception during the study and for 1 month following the last dose with ibrutinib or 12 months following the last dose with ofatumumab. Post menopausal females (>45 years old and without menses for >1 year) and surgically sterilized females are exempt from this criterion

10. Male patient must use an effective barrier method of contraception during the study and for 3 months following the last dose of study drug if sexually active with a female of childbearing potential
11. No history of stroke or intracranial hemorrhage within 6 months

7.3.4.2. Next-line Ibrutinib Therapy Treatment Phase

Refer to the next-line ibrutinib therapy Schedule of Assessments (Appendix M) for a complete list of procedures to be performed at each scheduled study visit.

8. MAIN EFFICACY EVALUATIONS

Disease evaluations will include:

- Physical examination (which will focus on the presence or absence or increase or decrease in lymph nodes, liver, and spleen).
- CBC with measurement of parameters by a central laboratory.
- Computed tomography (CT) scan of the neck, chest, abdomen, and pelvis (further timing is discussed in Section 7.3.2.7 and in the Schedule of Assessments [Appendix A]).

Efficacy assessments, for the purpose of the study result analyses, will be performed by an IRC blinded to study treatment information and independent of Investigators and personnel who are involved in the conduct of the study. The process and convention of the IRC will be detailed in a separate charter.

8.1. Definitions

8.1.1. Refractory

Refractory is defined as treatment failure or progression within 12 months post-treatment.

8.1.2. Relapsed

Relapsed is defined as a patient who met criteria for CR or PR, but progressed beyond 12 months post-treatment.

8.1.3. Treatment Failure

Treatment failure is defined as best response of progressive disease or SD while on study treatment.

8.1.4. Measurable Disease

Patients must have at least 1 measurable site of disease to participate in this study. Measurable sites of disease are defined as lymph nodes, or lymph node masses. Each measurable site of

disease must be greater than 1.5 cm in the longest diameter. Measurement must be determined by imaging evaluation.

Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If there are tumor lesions in previously irradiated areas and progression has occurred, these lesions will be considered measurable. If tumor lesions in previously irradiated areas are present and have been stable, then these lesions are not considered measurable. If tumor lesions in previously irradiated areas progress during the study, then disease progression will be considered as having occurred provided progression is confirmed by IRC.

All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures, as necessary, including peripheral blood counts.

8.1.5. Treatment-related Lymphocytosis

Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of ≥50% compared to baseline and ≥5000/μL that occurs in the setting of unequivocal improvement in at least one other disease-related parameter including lymph node size, spleen size, hematologic parameters (Hgb or platelet count), or disease-related symptoms. Given the known mechanism of action of BCR-inhibiting agents including ibrutinib, treatment-related lymphocytosis is an expected and frequent pharmacodynamic phenomenon observed with initiation (or re-initiation) of ibrutinib.

Response assessment in CLL patients treated with novel agents has been clarified by the authors of the IWCLL 2008 guidelines and is outlined in the NCCN NHL 2012 guidelines, supporting that patients with isolated lymphocytosis in the setting of improvement in other disease parameters should not be considered to have progressive disease or treatment failure (Cheson 2012).

8.1.6. Richter's Transformation

Richter's syndrome (RS) is lymphomatous transformation to a more aggressive histology in a patient with CLL or SLL. RS is most often characterized by the development of high-grade NHL or Hodgkin's disease. Symptoms of Richter's transformation can include new or progressive lymphadenopathy or organomegaly, fever, loss of weight and muscle mass, and other health problems. Richter's transformation can be suggested by a CT/PET scan, but should be confirmed with a biopsy (eg, lymph node) demonstrating the histologic transformation whenever possible.

8.1.7. Minimal Residual Disease (MRD)

Patients who have achieved a CR should be evaluated for eradication of disease cells as determined by flow cytometry on the bone marrow aspiration when available.

8.2. Radiographic Images Assessment

Radiological efficacy assessments, for the purpose of the study result analyses, will be performed by the IRC, which will be blinded to study treatment information. The process and convention of the review will be detailed in a separate charter.

The baseline disease assessment will include all areas of known and suspected disease with use of the most appropriate and reproducible radiological technique.

8.3. Guidelines for Evaluation

Table 3 outlines what is required for each parameter at baseline to be evaluable throughout the study.

Table 3: Evaluable Parameter Requirements

Parameter	Requirements to be Evaluable for Response
Measurable Disease (required for all patients)	Lymph Node > 1.5cm
Splenomegaly	Enlarged spleen
Hepatomegaly	Enlarged liver
Absolute Lymphocyte Count (ALC)	≥ 4,000 /µL
Platelets	≤100,000 /µL
Absolute Neutrophil Count (ANC)	≤ 1500 /µL
Hgb	≤ 11.0 g/dL

8.4. Response Categories

Assessment of response should include physical examination, radiographic imaging, and evaluation of blood and marrow per the schedule of assessments (see Appendix A and Appendix M) and to confirm CR. Definition of response for CR, CRi, nPR, PR, PR with lymphocytosis, and disease progression will be evaluated by the criteria listed in Table 4. Category A criteria define the tumor load and Category B criteria define the function of the hematopoietic system. Response must be confirmed by CT and central labs, and must last at least 2 months without transfusional support or growth factor product to be considered a confirmed response.

8.4.1. Complete Response (CR)

All of the following are required for a CR:

- No significant lymphadenopathy (>1.5cm) palpable on examination or by CT
- No hepatosplenomegaly on examination or by CT

- No constitutional symptoms (ie, no fever >38ºC for ≥2 weeks, no unintentional ≥10% body weight loss within last 6 months, no night sweats for >1 month without other evidence of infection, no fatigue interfering with work or usual activities)
- Neutrophils >1.5 x10^9/L, platelets >100,000/μL, and Hgb >11g/dL without recent growth factor or transfusions
- ALC <4,000 /μL

Marrow aspirate and biopsy must be performed after all other criteria meet the definition of CR. To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. B-lymphoid nodules should be absent. In addition, in patients with a CR, MRD by flow cytometry should be performed to evaluate MRD status.

Table 4: Criteria for Response Categories

Parameter	CR	PR	PD
Group A			
Lymphadenopathy[a]	None; ≤1.5cm	Decrease ≥50%	increase ≥50%
Hepatomegaly	None	Decrease ≥50%	increase ≥50% or new hepatomegaly
Splenomegaly	None	Decrease ≥50%	increase ≥50% or new splenomegaly
Blood lymphocytes	<4000/µL	Decrease ≥50% from baseline	increase ≥50% over baseline[c]
Marrow[b]	Normocellular, <30% lymphocytes, no B lymphoid nodules, Hypocellular defines CRi		
Group B			
Platelet count	>100,000/µL	>100,000/µL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Hemoglobin	>11 g/dL	>11g/dL or increase ≥50% over baseline	Decrease of >2g/dL from baseline secondary to CLL
Neutrophils	>1500/µL	>1500/µL or increase ≥50% over baseline	N/A

[a] Sum of the products of multiple lymph nodes (as evaluated by CT scans) or the longest diameter of one target lymph node

[b] This parameter is not relevant for the PD category unless confirming cytopenic progression.

[c] Patients with treatment-related lymphocytosis should remain on study treatment in the absence of other criteria for progressive disease (see Section 8.1.5).

Note: Group A defines the tumor load and Group B defines the function of the hematopoietic system

CR: all of the criteria need to be met and patients have to lack disease related constitutional symptoms. Bone marrow and aspirate is required to confirm CR.

PR: all abnormal Group A criteria must be met plus 1 of the criteria from Group B must be met. Note if all PR criteria with the exception of ALC are met this is consistent with a PR with lymphocytosis

SD: the absence of PD and the failure to achieve a CR, CRi, nPR, PR, or PR with lymphocytosis.

PD: at least 1 of the above criteria from Group A or B are met or development of transformation to a more aggressive histology

Cross reference: Hallek 2008 and Hallek et al. June 2012 e-letter

8.4.2. Complete Response with an Incomplete Marrow Recovery (CRi)

CRi is defined as a CR with an incomplete recovery of the patient's bone marrow. Patients who have a CRi fulfill all criteria for a CR, but continue to have persistent anemia, thrombocytopenia, or neutropenia. These cytopenias are due to drug toxicity in the bone marrow and are not due to any evidence of CLL. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or when peripheral blood counts have recovered. However, this time interval should not exceed 6 months.

8.4.3. Nodular Partial Response (nPR)

nPR is a response where patients meet criteria for a CR, but the bone marrow biopsy shows that there are still B-lymphoid nodules, which may represent a clonal infiltrate. These nodules are residual disease and therefore the patient is termed an nPR.

8.4.4. Partial Response (PR)

A ≥50% drop in lymphocyte count from baseline or ≤4.0 x 10^9/L is required for a PR and all of the following are observed:

- ≥50% decrease in the sum products of up to 6 lymph nodes, a ≥50% decrease in the longest diameter of the single lymph node, or normalization of lymphadenopathy when compared to baseline.
- No new enlarged lymph nodes by physical examination or CT AND no increase in any lymph node by CT. Note: In a small lymph node <2 cm, an increase of less than 25% is not considered to be significant.
- When abnormal, a ≥50% decrease in the enlargement of the spleen and/or liver from baseline or normalization by CT

Plus a response in at least one of the following evaluable criteria independent of growth factor support or transfusion.

- Neutrophils >1.5 x10^9/L, or ≥50% improvement over baseline
- Platelets >100,000/μL or ≥50% improvement over baseline
- Hgb >11 g/dL or ≥50% improvement over baseline

  * Note: If all criteria are normal, defined as neutrophils >1.5 x10^9/L, platelets >100,000/μL, and Hgb >11g/dL at baseline, they must remain normal to be considered consistent with a PR.

8.4.5. PR with Lymphocytosis

Patient achieved all PR criteria with the exception of lymphocyte criteria.

8.4.6. Stable Disease (SD)

Not meeting criteria for CR, CRi, nPR, PR, PR with lymphocytosis, or progressive disease.

8.4.7. Progressive Disease

A CT scan is required to evaluate all cases of suspected progressive disease for this protocol regardless of the modality of disease progression (eg. lymph node, lymphocytosis, or transformation). Progressive disease requires at least ONE of following:

- New enlarged nodes >1.5 cm, new hepatomegaly or splenomegaly; or other organ infiltrates
- ≥50% increase from nadir in existing lymph node (must reach >1.5 cm in the longest diameter) or ≥50% increase from nadir in sum of product of diameters of multiple nodes
- ≥50% increase from nadir in enlargement of liver or spleen
- ≥50% increase from baseline in lymphocyte count (and to ≥5 x10^9/L) unless considered treatment-related lymphocytosis (Section 8.1.5)
- New cytopenia (Hgb or platelets) attributable to CLL. The progression of any cytopenia (unrelated to autoimmune cytopenia, drugs, or bleeding), as documented by a decrease of Hgb levels from baseline by more than 20 g/L (2g/dL) or to less than 100 g/L (10g/dL) and lower than baseline, or by a decrease of platelet counts from baseline by ≥50% or to less than 100 × 10^9/L (100,000/µL) and lower than baseline in the presence of active CLL, defines disease progression ; a marrow biopsy must demonstrate an infiltrate of clonal CLL cells if no other evidence of disease progression is present on CT scan.
- Transformation to a more aggressive histology (eg, Richter's Transformation). Whenever possible, this diagnosis should be established by biopsy.

Suspected progressive disease must be confirmed by a serial exam at least 2 weeks later. Please see Section 7.1.31 on details regarding suspected PD and IRC confirmation.

8.5. Sustained Hematological Improvement

In the subset of patients with cytopenia(s) at baseline (Hgb ≤11g/dL, platelets ≤100,000/µL, or ANC ≤1500/µL), time to improvement in blood counts and percentage of patients with sustained improvement in blood counts, (sustained improvement, defined as improvement in cytopenia by ≥50%, or Hgb >11g/dL, ANC >1500 cells/µL, platelets >100,000/µL with the duration of improvement lasting for at least 2 months without blood transfusion or growth factors), will be recorded.

8.6. Resolution of Pretreatment Disease-related Symptoms

Resolution of pretreatment symptoms including fatigue, weight loss, anorexia, fevers, night sweats, or symptoms of splenomegaly will be evaluated.

9. ASSESSMENT OF SAFETY

9.1. Safety Monitoring Plan

The safety of this study will be assessed by an independent DMC. All enrolled patients will be evaluated clinically and using standard laboratory testing during their participation in this study.

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

9.2. Definitions

9.2.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

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

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

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.
- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL/SLL that were not present before the AE reporting period (see Section 9.3.1)
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.

- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

9.2.2. Serious Adverse Event

Note: The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition.

A SAE (experience) or reaction is any untoward medical occurrence that at any dose:

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

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

9.2.3. Severity

Definitions found in the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) will be used for grading the severity (intensity) of nonhematologic AEs. Refer to Appendix D for the grading of hematologic AEs. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE v4.0, the following grading system should be used to assess severity:

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

9.2.4. Causality

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

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

9.2.5. Unexpected Adverse Events

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

9.3. Documenting and Reporting of Adverse and Serious Adverse Events by Investigators

The Investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF. All SAEs also must be reported on the SAE Worksheet (see Section 9.3.3).

9.3.1. Adverse Event Reporting Period

All adverse events will be reported from the time the patient signs the Informed Consent Form until 30 days following the last dose of study drug.

If an SAE is present at the End-of-Treatment Visit, the SAE should be followed to resolution or until the Investigator assesses the patient as stable, or the patient is lost to follow-up or withdraws consent. Resolution/stable means the patient has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

If a death occurs within 30 days after the last dose of study drug, the death must be reported to the Sponsor as an SAE.

Any SAE that occurs more than 30 days after the last dose of the study drug and is deemed related to ibrutinib, must be reported to the sponsor.

9.3.2. Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation timepoints during the study. All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means will be recorded in the patient’s medical record and on the AE CRF and, when applicable, on the SAE Worksheet.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

9.3.3. Expedited Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on the SAE Worksheet and faxed to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the Investigator (eg, hospital admission/discharge notes and laboratory results). The contact information (phone, fax and email) for the drug safety can be found on the SAE Worksheet form and instructions.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report or the adverse event/SAE most proximal to death should be the term reported. Autopsy and postmortem reports must be forwarded to Pharmacyclics Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

9.3.4. Events of Special Interest

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to the Sponsor within 24 hours of awareness following the procedure described above for SAEs (Section 9.3.3) and will require enhanced data collection. **All Events of Special Interest will be submitted without a serious criterion selected if no other serious criterion is met.**

9.3.4.1. Major Hemorrhage

Defined as any hemorrhagic event that is Grade 3 or greater in severity, or that results in one of the following: intraocular bleeding causing loss of vision, the need for a transfusion of two or more units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of hospitalization.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 9.3.4 above.

9.3.4.2. Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest according to Section 9.3.4 above.

9.3.5. Other Malignancies

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

9.3.6. Pregnancy

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

A female patient must immediately inform the investigator if the patient becomes pregnant from the time of consent to 30 days after the last dose of ibrutinib or to 12 months following the last dose of ofatumumab. A male patient must immediately inform the investigator if the patient's partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female patients receiving ibrutinib capsules who become pregnant must immediately discontinue study drug. The Investigator should counsel the patient, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Report any pregnancy that occurs in a patient or patient's partner from the time of consent to 30 days after the last dose of study drug. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. With consent the pregnant female will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as an SAE.

9.3.7. Eye-Related Adverse Events

New or worsening eye-related symptoms that are Grade ≥2 should be evaluated by an ophthalmologist whose findings should be reported on the ophthalmic CRF.

9.4. Reporting of Serious Adverse Events by Sponsor

Regulatory Authorities, IRBs/REBs/IECs, and Investigators will be notified of SAEs in accordance with applicable requirements (eg, Good Clinical Practices [GCPs], ICH guidelines, national regulations, and local requirements).

The Pharmacyclics Pharmacovigilance Committee will review and evaluate accumulating safety data from the entire clinical trial database for ibrutinib at appropriate intervals (eg, quarterly) to identify new safety signals or increased frequency of events. This will include an aggregate review and comparison to the control group of SAEs that were deemed as "not suspected" of being associated with use of ibrutinib because they were likely to have been manifestations of underlying disease or that commonly occur in the patient population.

10. WITHDRAWAL OF PATIENT FROM TREATMENT OR STUDY

Investigators are encouraged to keep a patient experiencing clinical benefit on study treatment unless significant toxicity puts the patient at risk or routine noncompliance puts the study outcomes at risk.

10.1. Discontinuation of Treatment

If the patient meets any of the following criteria then discontinuation from treatment is mandatory:

- Progressive disease as determined by protocol defined criteria
- Toxicity as defined in dose discontinuation portions of the protocol
- Death
- Withdrawal from treatment by patient including withdrawal of informed consent
- Investigator decision
- Completion of treatment regimen (applies to ofatumumab only)
- Requires prohibited treatment
- Lost to follow-up
- Study terminated by Sponsor

10.2. Withdrawal from the Study

A patient may be withdrawn from the study for any of the following reasons including:

- Death
- Lost to follow-up
- Study terminated by Sponsor
- Withdrawal of consent
    - Withdrawal of consent is the primary reason for study termination only if a patient refuses any further contact or follow up. Please contact Medical Monitor within 24 hours of any consent withdrawal.

In case a patient is lost to follow-up, every possible effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation. The measures taken to follow-up must be documented in the patient's records.

When a patient withdraws before completing the study, the reason for withdrawal must be documented in the source documents.

10.3. Extension Study

Patients who were on study drug and did not progress at the time of study closure may enroll into a long-term extension study and continue to receive ibrutinib when access to commercial ibrutinib is not feasible.

11. ENDPOINTS

11.1. Primary

The primary endpoint of the study is PFS, as assessed by IRC review per IWCLL 2008 criteria (Section 8.4).

11.2. Secondary

Efficacy

To compare between the two treatment groups in terms of:

- OS
- Overall response rate (ORR) is defined as the proportion of patients who achieve complete response (CR), complete response with incomplete bone marrow recovery (CRi), nodular partial response (nPR), or partial response (PR) per IWCLL 2008 criteria over the course of the study as evaluated by an IRC
- Patient reported outcome (PRO) as measured by the FACiT-Fatigue.
    - The efficacy measure for the FACiT-Fatigue will be the change in scores from baseline to each assessment.
- Hematological improvement in the subset of patients with cytopenia(s) at baseline assessed by time to improvement and percentage of patients with improvement

Safety

- To compare the safety and tolerability between the two treatment groups

11.3. Exploratory

- Investigator-assessed PFS per IWCLL 2008 criteria
- Investigator-assessed ORR per IWCLL 2008 criteria
- Improvement of disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain due to splenomegaly, or anorexia).
- Patient reported outcomes (PRO) as measured by EORTC QLQ-C30 and EQ-5D-5L.
    - The efficacy measure for the EORTC QLQ-C30 will be the change in scores from baseline to each assessment for all scales.

- The efficacy measure for the EQ-5D-5L will be the change in weighted utility score from baseline to each assessment.

- Medical resource utilization (MRU) associated with the therapy including the number of hospitalizations, emergency department visits, blood product transfusions, and use of hematopoietic growth factors.
- PK characteristics of ibrutinib in patients with CLL/SLL and to determine which, if any, covariates (eg, age, gender, body size, race) influence exposure to ibrutinib.
- Exploratory evaluation of predictive biomarkers and/or mechanisms of resistance.

12. STATISTICAL CONSIDERATIONS

This section outlines statistical analysis approaches and methods for the study. Specific details for efficacy and safety analyses will be described in the Statistical Analysis Plan (SAP).

12.1. General Considerations

12.1.1. Independent Review Committee (IRC)

The IRC will be chaired by a physician with expertise in CLL and SLL and will conduct response evaluations in accordance with the IRC charter.

12.1.2. Data Monitoring Committee (DMC)

The safety of this study will be monitored by an independent DMC.

An early safety analysis will be performed after approximately 50 patients have been treated for approximately 8 weeks. This analysis will focus on deaths, treatment discontinuations, SAEs, and grade 3/4 AEs as well as special events of interest. This information will be reviewed by the Medical Monitor on an ongoing basis until this early safety analysis is conducted. The chair of the DMC, with involvement of the DMC statistician, as needed, will issue a recommendation as to whether the study should be interrupted during this period. If the DMC recommends the trial be continued, the DMC will review safety data every 6 months. Otherwise, the DMC may request further safety analyses. Results from a pre-specified interim analysis will also be reviewed by the DMC.

The independent DMC will be chaired by a physician with expertise in CLL and SLL. The DMC will review data and provide recommendations regarding stopping or continuing the trial in accordance with the DMC charter. The Sponsor may attend only the blinded portion of the DMC meetings to answer questions as necessary. The DMC charter will provide provisions for restricted communications between the DMC and the Sponsor in the event the DMC recommends stopping the study for safety or superiority. Following the DMC review of the prespecified interim analysis and the unanimous recommendation that the study be stopped early and patients on ofatumumab be provided access to ibrutinib – the DMC reviews have concluded.

12.2. Randomization

Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, randomization will be stratified using the following two stratification factors and patients will be randomized in a 1:1 ratio to receive either ofatumumab or ibrutinib within each randomization stratum:

a) The presence or absence of disease that is refractory to purine analog and anti-CD20 containing chemoimmunotherapy regimen (at least 2 cycles). Refractory is defined as treatment failure (best overall response of SD or progressive disease on treatment) or disease progression within 12 months of the last dose of purine analog.

b) The presence or absence of 17p del as determined by the assay specification on pretreatment FISH or cytogenetics evaluation.

12.3. Sample Size considerations

This study is designed to evaluate PFS and is powered based on this endpoint. Therefore, the desired operating characteristics for the PFS endpoint are used to determine the study's total sample size and overall duration.

With the agreement from the European (Rapporteur and Co-Rapporteurs) and US Health Authorities, the overall two-sided significance level for this study is revised from 0.01 to 0.05. Given this revision in overall significance level, 176 PFS events provides approximately 90% power to detect the target hazard ratio of 0.6 based on a log-rank test and a two-sided overall significance level of 0.05 adjusted for one planned interim analysis.

The sample size and power calculations are based on a two-sided log-rank test for PFS and a two-sided log-rank test for OS and were calculated using the software package East 5.4 (Cytel Software Corp., Cambridge, MA).

12.4. Interim Analysis

A pre-specified interim analysis for both superiority and futility (non-binding) will be performed after approximately 117 IRC confirmed PFS events are reported. Futility will be evaluated by a one-sided test. One-hundred and seventeen (117) PFS events correspond to 66.5% of the revised planned number of PFS events (176) for the final analysis. Lan-DeMets spending function with O'Brien-Fleming boundary will be used as an early stopping guidance (O'Brien 1979). At the interim analysis, the alpha spending for PFS will be determined based on the actual information fraction using O'Brien-Fleming boundary. Significance level for all secondary endpoints except OS will be adjusted with the same significance level as for PFS at the interim analysis. The two sided significance level for OS will be 0.03 at the interim analysis. The independent DMC will review the interim PFS analysis results and make a recommendation accordingly. Details regarding interim efficacy analysis will be described in the DMC charter and the SAP.

12.5. Final Analysis

The final analysis for the PFS will be conducted after approximately 176 PFS events are confirmed by the IRC. The two-sided significance level for the final analysis for primary and all secondary endpoints will be adjusted to account for interim alpha spending so the overall two-sided significance level for the study will be preserved at 0.05.

12.6. Analysis Populations

12.6.1. Intent-to-Treat (ITT) Population

The ITT population is defined as all patients who were randomized. All efficacy analysis will be performed using the ITT population and patients in the ITT population will be analyzed as randomized. In addition, ITT population will be used to summarize demographics, and baseline and disease characteristics.

12.6.2. Safety Population

The safety population includes all patients who received at least one dose of study drug. The safety analysis will be performed using the safety population and patients in the safety population will be analyzed as treated.

12.6.3. Pharmacokinetic (PK) Evaluable Population

Pharmacokinetic (PK) evaluable population includes patients who received at least 1 dose of study drug and had at least one post-treatment sample obtained.

12.6.4. Biomarker Population

Biomarker population includes patients whose biomaterial is available and who have consented to participate in the study's biomarker evaluation.

12.7. Control for Bias

The following study design components will facilitate the control for bias:

- Large (approximately 350 patients)
- Multicenter
- Randomized

The randomization code will be controlled through a centralized procedure and will not be known to sponsor personnel directly involved with study conduct or data analysis until after the interim analysis (if early stopping for superiority) or final analysis. The unblinding procedure will be described in detail in the study unblinding plan.

12.8. Efficacy Analyses

All the stratified analyses will be based on the two randomization stratification factors: 1) refractory disease (presence versus absence) to purine analog and anti-CD20 containing chemoimmunotherapy regimen, and 2) status of 17p del (presence versus absence).

12.8.1. Primary Endpoint and Methods

The primary efficacy endpoint is PFS, which is defined as the time from the date of randomization until disease progression (assessed by the IRC per IWCLL 2008 criteria) or death from any cause, whichever occurs first. Patients who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. For patients without an adequate post-baseline disease assessment, PFS will be censored on the date of randomization.

The primary efficacy analysis will be performed in the ITT population to compare PFS as assessed by the IRC for the two treatment arms using a stratified log rank test. Distribution of PFS will be summarized for each treatment arm using median and its corresponding 95% confidence interval based on Kaplan-Meier estimates. The estimate of the hazard ratio and its corresponding 95 percent confidence interval will be computed using a Cox Proportional Hazards model stratified by the two randomization stratification factors.

12.8.2. Secondary Endpoints and Methods

12.8.2.1. Overall Survival (OS) and Survival Rate at Landmark Points

Patients will be followed for survival status until end of study.

OS is defined as the time from date of randomization until date of death due to any cause. Patients who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. Patients who are completely lost to follow-up for survival will be censored at randomization date.

The analysis methods for overall survival will be similar to those described for PFS.

In addition, survival rate at landmark points will be summarized for each treatment arm using Kaplan-Meier point estimates and compared using the standard normal Z test.

12.8.2.2. Overall Response Rate

Overall response rate (ORR) is defined as the proportion of patients who achieve a CR, CRi, nPR, or PR over the course of the study as evaluated by the IRC using IWCLL 2008 criteria. Patients who do not have any post-baseline response assessment will be considered as non-responders. A Cochran-Mantel-Haenszel chi-square test, stratified by the two randomization stratification factors, will be used to compare the two treatment arms.

12.8.2.3. Patient-Reported Outcome (PRO) Measures

PRO as measured by FACiT-Fatigue will be summarized as the change in scores from baseline to each assessment.

12.8.2.4. Hematological Improvements

In the subset of patients with cytopenia(s) at baseline (Hgb ≤11 g/dL, platelets ≤100,000/μL, or ANC ≤1500/μL), time to sustained improvement and percentage of patients with sustained hematological improvement will be measured. Sustained hematological improvement is defined as improvement in cytopenia by ≥50%, or Hgb >11 g/dL, ANC >1500/μL, platelets >100,000/μL with the duration of improvement lasting for at least 2 months without blood transfusion or growth factors.

- Time to sustained improvement in blood count will be compared using unstratified log rank test. The distribution of the time to sustained improvement will be summarized using Kaplan-Meier estimates.
- Percentage of patients with sustained improvement will be compared using χ^2 test.

12.8.3. Exploratory Endpoints and Methods

12.8.3.1. Investigator-Assessed PFS

Investigator-assessed PFS is defined as time from randomization until disease progression (assessed by the Investigator per IWCLL 2008 criteria) or death from any cause, whichever occurs first.

Analysis methods for Investigator-assessed PFS will be similar to those described for PFS as assessed by the IRC.

12.8.3.2. Investigator-Assessed ORR

Investigator-assessed ORR will be summarized and analyzed similarly to IRC-assessed ORR.

12.8.3.3. Improvement of Disease-related Symptoms

Disease-related symptoms including weight loss, fatigue, fever, night sweats, abdominal pain due to splenomegaly, or anorexia) will be assessed by at each assessment compared to baseline. Percentage of patients with improvement will be compared using χ^2 test.

12.8.3.4. Patient-Reported Outcome (PRO) Measures

Patient Reported Outcome (PRO) measures include EORTC QLQ-C30 and EQ-5D-5L.

For EORTC QLQ-C30, change in scores from baseline to each assessment will be summarized.

For EQ-5D-5L, change in weighted utility score from baseline to each assessment will be summarized. The scores for the five categorical dimensions will be used to compute a single utility score ranging from zero (0.0) to one (1.0) representing the general health status of the patient. The United Kingdom weights will be used to generate patient utilities from the 5 dimensions.

12.8.3.5. Biomarker Analysis

Analyses are to identify biomarkers that are predictive of response (or resistance) to ibrutinib. Analyses will be performed within each treatment group in total and stratified by clinical covariates or molecular subgroups. The associations of biomarkers with clinical response or time-to-event endpoints will be assessed using the appropriate statistical methods (analysis of variance [ANOVA], categorical, or survival model), depending on the endpoint. Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints will identify responsive (or resistant) subgroups.

12.8.3.6. Medical Resource Utilization (MRU) Associated with the Therapy

Parameters collected for MRU associated with the therapy include number of hospitalizations, number of emergency department visits, number of blood product transfusions, and number of use of hematopoietic growth factors. Those parameters will be summarized with descriptive statistics by treatment arm.

12.8.3.7. Pharmacokinetic (PK) Analysis

The plasma concentration data for ibrutinib will be summarized using descriptive statistics at each timepoint. Population PK analysis of plasma concentration-time data of ibrutinib will be performed using nonlinear mixed-effects modeling. Data may be combined with data from other studies to support a relevant population PK model. Available patient characteristics (eg, demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

12.9. Safety Analyses

Safety summaries will include tabulations in the form of tables and listings. The safety analysis will be conducted using the safety population. Patients will be analyzed according to the actual treatment received.

Study drug exposure including duration and dosage as well as dose modifications of study drug including dose reduction, dose delay, missed doses, and dose interruption will be summarized.

12.9.1. Adverse Events (AEs)

Adverse events (AEs) will be graded by the Investigator according the NCI CTCAE v4.0 for non-hematological AEs. Hematologic toxicity will be assessed by the IWCLL 2008 criteria for grading hematologic toxicity in CLL studies. Verbatim descriptions of AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events that started from the date of the first dose of study drug up to 30 days after the date of the last dose of study drug are considered treatment-emergent. All-treatment emergent AEs will be summarized by treatment arm. The incidence rates of treatment-emergent AEs will be summarized by System Organ Class (SOC), preferred term, toxicity grade, and relationship to study drug. In addition, SAEs, Grade 3 or above AEs, AEs leading to study treatment discontinuation, delay, reduction, or interruption, AEs leading to death, and events of special interest will be summarized. Multiple occurrence of the same event in a given patient will be counted once at the maximum severity and strongest relationship to study drug.

AEs leading to death and non-fatal SAEs will be listed by patient and tabulated by preferred term.

12.9.2. Laboratory Evaluations

All laboratory values will be converted to standard international (SI) units and classified as normal, low, or high based on normal ranges supplied by the central laboratory. Hematologic parameters including platelet count, hemoglobin, and neutrophils will be assessed by the IWCLL 2008 criteria for grading hematologic toxicity in CLL studies. All other gradable laboratory parameters will be graded using the NCI CTCAE v4.0.

Patients with values outside the normal range will be flagged and summarized by treatment arm. Selected gradable laboratory parameters will be summarized by treatment arm using shift tables. A separate listing and table will be provided to identify and summarize patients with markedly abnormal changes. In addition, changes from baseline in quantitative parameters will be summarized descriptively by treatment arm at scheduled timepoints.

12.9.3. Vital Signs

Vital signs will be classified as normal, low, or high and change from baseline will be summarized descriptively by treatment arm at scheduled timepoints. Patients with markedly abnormal changes will be listed and tabulated.

12.9.4. Other Safety Assessments

Physical examination, ECG, and eye examination results will be listed.

13. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

13.1. Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

13.2. Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The Investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (eg, all advertising materials or materials given to the patient during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and informed consent form must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

The Investigator is responsible for providing the IRB/REB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/REB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative before entering patients in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

13.3. Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the Investigator or his/her designee provides to the patient and the patient's agreement to participate.

The Investigator or designee (designee must be listed on the Delegation of Authority log), **must** explain in terms understandable to the patient the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the patient's source record. Each patient must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each patient's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the patient at the time that it is signed by the patient.

13.4. Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

13.5. Protected Patient Health Information Authorization

Information on maintaining patient confidentiality in accordance to individual local and national patient privacy regulations must be provided to each patient as part of the informed consent process (refer to Section 13.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The Investigator or designee **must** explain to each patient that for the evaluation of study results, the patient's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics will not use the patient's protected health information or disclose it to a third party without applicable patient authorization. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each patient. If a patient withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the patient **and** to ensure that no further data will be collected from the patient. Any data collected on the patient before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the patient will be respected with strict adherence to professional standards and regulations.

13.6. Study Files and Record Retention

The Investigator **must** keep a record that lists **all** patients considered for enrollment (including those who did not undergo screening) in the study. For those patients subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The Investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/REB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including patient confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections, SAE forms

transmitted to Pharmacyclics and notification of SAEs and related reports, source documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the Investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The Investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics before destroying any clinical study documents or images (eg, scan, radiograph, ECG tracing) at any time. Should an Investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the Investigator of the date that study records may be destroyed or returned to Pharmacyclics.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the Investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the Investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the Investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the Investigator for audit purposes.

13.7. Case Report Forms and Record Maintenance

Case report forms (CRFs) will be used to collect the clinical study data and must be completed for each enrolled patient with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed within 5 days of each patient's visit. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exists within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system. After database lock, the Investigator

will receive a copy of the patient data (eg, paper, CD, or other appropriate media) for archiving at the study site.

13.8. Investigational Study Drug Accountability

Ibrutinib and any comparator used must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply ibrutinib or comparator to other Investigators, patients, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

Accountability records for ibrutinib and any comparator must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. Study identification number (PCYC-1112-CA)
2. Patient identification number
3. Lot number(s) of ibrutinib or comparator dispensed for that patient
4. Date and quantity of drug dispensed
5. Any unused drug returned by the patient

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

13.9. Study Monitoring/Audit Requirements

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also patient to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all patients during this clinical study. However, because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/REB/IEC, representatives of Pharmacyclics, its designated agents and authorized employees of the appropriate Regulatory Authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all patients enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

13.10. Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol; will read and understand the IB; will obtain IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

13.11. Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform Investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

13.12. Financial Disclosure

A separate financial agreement will be made between each Principal Investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each Investigator and Subinvestigator (as designated on the Form FDA1572) will provide a signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

13.13. Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the Investigator/ designee will be provided.

If a bodily injury is sustained, resulting directly from the use of the study drug, Pharmacyclics will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which is not covered by the patient's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the Investigator/ study staff. The ICF will include a description of this reimbursement policy, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

13.14. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/REB/IEC and required site approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand and sign any revised ICF confirming willingness to remain in the trial.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the Investigator and Pharmacyclics.

13.15. Publication of Study Results

Pharmacyclics may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

In most cases, the Investigators at the sites with the highest accruals of eligible patients shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Pharmacyclics.

13.16. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the Investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patients' interests.

14. REFERENCE LIST

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15. APPENDICES

Appendix A: Schedule of Assessments

			Treatment Phase												Follow-Up Phase	
Study Weeks		**Screening Phase**	1	2	3	4	5	6	7	8	12-24 **q4 weeks**	36 until tx term **q12 weeks**	Response Evaluations[c] **q12 weeks until PD**	**End-of-Treatment visit** 30 days after last dose of study drug	Post-treatment Phase[c] **q12 weeks until PD**	Post-disease Progression Phase **q12 weeks**
Study Windows		*-28 days*	*± 3 days*										*± 7 days*	*± 3 days*	*± 7 days*	*± 7 days*
Study Drug Administration																
ARM A	Ofatumumab 300 mg IV		x													
	Ofatumumab 2000 mg IV			i	i	x	i	i	i	x	x					
ARM B	Ibrutinib 420 mg/day PO		Continuous Daily Dosing													
Procedures																
Informed consent		x														
Confirm eligibility & randomize		x	x													
Medical history		x	x													
Physical exam & ECOG status		x	x			x				x	x	x		x	x	
Vital signs		x	x			x				x	x	x		x		
ECG		x	If clinically indicated (eg, subjects with palpitations, lightheadedness)													
Coagulation (PT, INR, and aPTT)		x														
Eye-related symptoms		x									x[d]	x[c]		x		
PRO assessments		x				x				x	x	x		x	x	
Disease-related symptoms[g]			x			x				x	x	x		x	x	
Cumulative Illness Rating Scale (CIRS)[a]			x													
Concomitant medications		x	x	x	x	x	x	x	x	x	x	x		x		
Adverse events		x	x	x	x	x	x	x	x	x	x	x		x		
Pregnancy test		x														
Hepatitis serologies		x														
Cytogenetic, CLL FISH panel		x (-90 days*)														
Hematology		x	x	x	x	x	x	x	x	x	x	x		x	x	
Serum chemistry		x	x			x				x	x	x		x		
Serum immunoglobulins & β_2-microglobulin			x								x[d]	x			x	
Sparse PK sample collection[f]			x			x[e]										
Genetic & molecular prognostic factors		x														
T/B/NK cells			x								x[d]	x			x	
Flow cytometry-based immunophenotype assays			x		x		x			x	x	x		x	x	
Predictive/resistance biomarkers			x		x		x					x		x	x	
CT scans		x (-6 wks*)											x[c]			
Medical resource utilization (MRU) [g]			x	x	x	x	x	x	x	x	x	x		x	x	x
Overall response evaluation													x[c]			
Bone marrow biopsy and/or aspirate[b]		x (-90 days*)											x[b]			
Survival status																x
Subsequent anticancer therapies															x	x

i = infusion visit only; * from randomization

a. Cumulative Illness Rating Scale (CIRS) for patients who are ≥65 years of age.
b. Bone marrow biopsy and aspirate should be obtained to confirm CR and to evaluate cytopenia.
c. Eye-related symptoms and overall response assessment will only need to be performed every 24 weeks after 18 months. CT scans will only need to be performed every 24 weeks after 12 months and annually after 36 months.
d. Weeks 12 and 24 only
e. Week 4 Sparse PK sample collection for ibrutinib arm only. If patient is unable to complete PK assessments at the Week 4 visit, it is acceptable to complete these assessments at the Week 8 visit.
f. Patients who must take strong or moderate CYP3A4/5 inhibitors while on treatment with ibrutinib, additional PK collections for evaluation of ibrutinib exposure is requested at the following scheduled visit after concomitant CYP3A4/5 inhibitor has started and still in use. Please refer to Section 7.1.21 for the PK collection schedules.
g. Starting from Amendment 5, data collection of disease-related symptoms and MRU will be suspended.

Appendix B: ECOG Status Scores

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

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

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Appendix C: Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.6.1.1 on instructions for concomitant use of CYP3A inhibitors or inducers with ibrutinib.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole [a]	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole [b]	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

Source: http://medicine.iupui.edu/clinpharm/ddis/main-table/

a. Based on PBPK simulations, up to 9.7-fold increase in AUC and 6.2-fold increase in C_{max} could be observed. If ibrutinib needs to be administered with posaconazole, 140 mg ibrutinib will be dosed.

b. Based on internal data, 140 mg ibrutinib dosed with voriconazole produces ibrutinib exposures similar to 560 mg ibrutinib dosed alone. Therefore, for this study, if ibrutinib needs to be administered with voriconazole, 140 mg ibrutinib will be dosed.

Appendix D: Hematologic Adverse Event Grading Scheme (Hallek 2008)

An evaluation of the hematologic toxicity in patients with advanced CLL/SLL must consider the high frequency of marrow involvement and previous exposure to chemotherapy with consequent medullary compromise at the initiation of therapy. The standard hematologic grading system for solid tumors cannot, therefore, be directly applied. A substantial proportion of patients would be considered to have Grade 2 to 4 hematologic toxicity before any therapy is given. Therefore, the following modified schema will be used to quantitate hematologic deterioration in patients with CLL/SLL.

Hematologic Grading Scheme

Decrease in Platelets or Hgb (Nadir) from Pre-treatment Value, %	ANC/µL (nadir)[c]	Toxicity Grade
0 - 10%[a]	≥ 2000	0
11 - 24%[a,b]	≥ 1500 and < 2000	1
25 - 49%[a,b]	≥ 1000 and < 1500	2
50 - 74%[a,b]	≥ 500 and < 1000	3
> 75%[a,b]	< 500	4

a. If at any level of decrease, the platelet count falls below 20×10^9/L, toxicity will be considered Grade 4. If the baseline platelet count is $<20 \times 10^9$/L, platelet toxicity cannot be evaluated.

b. Baseline and subsequent Hgb values must be determined the day of any given transfusion.

c. If the ANC was < 1000/µL before therapy, the patient is not evaluable for toxicity referable to the ANC.

Appendix E: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix F: EQ-5D-5L

(English version for the UK)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

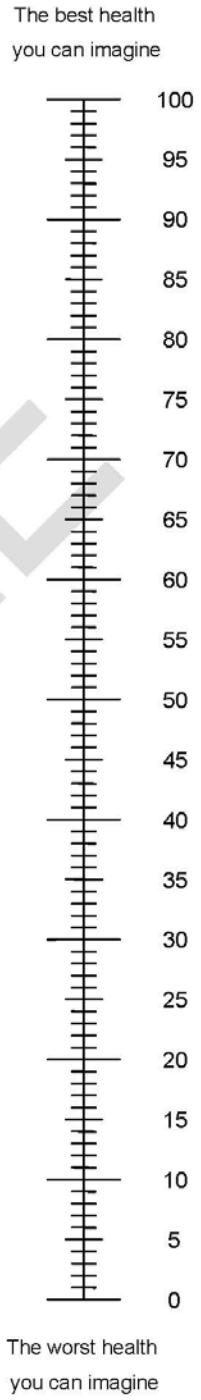
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix G: FACiT-Fatigue

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix H: Cumulative Illness Rating Scale (CIRS)

CIRS is an indicator of illness severity and comorbidity in older patients (Extermann, 1998)[1].

CIRS scoring is to be performed in the setting of a pretreatment comprehensive history and physical by a licensed provider (nurse, PA, MD, or DO) for all patients 65 years and older.

Instructions:

The following pages include the CIRS scoring worksheet displaying 14 organ-system categories. Write brief descriptions of the medical problem(s) that justified the endorsed score on the line following each item. Circle the appropriate score from 0 – 4 based on the rating strategy. Space is provided in each system organ class to provide written descriptions.

1. Complete each category score as identified by the rating strategy on the worksheet
2. Each category has room for written comments. If additional room is needed, please document on the back of the form
3. Add the number of **Total Categories Endorsed** (measured)
4. Provide the **Total Score**
5. Provide the **Severity Index** (total score divided by total number of categories endorsed)
6. Provide the number of categories at **level 3 severity**
7. Provide the number of categories at **level 4 severity**

CLL Rating:

Please take into account that CLL/SLL diagnosis itself or induced illness or organ damage (including cytopenias) are not included in this rating scale. The goal of this rating scale is to assess comorbidity other than CLL/SLL in the patient.

[1] Extermann M, Overcash J, Lyman GH, Parr J, Balducci L, Comorbidity and functional status are independent in older patients. J Clin Oncol 1998; 16: 1582–87.

PCYC 1112-CA Scoring Sheet CIRS(G)

Cumulative Illness Rating Scale for Geriatrics[2]

Patient ID# _____ Site # _____ Investigator: _____

Rater Name: _____ Date: ___/___/___
***Note Rater must be on delegation of authority log**

Rating Strategy

Please see specific scoring guidelines below for each organ system.

0 – No Problem

1 – Current mild problem or past significant problem

2 – Moderate disability or morbidity/requires "first line" therapy

3 – Severe/constant significant disability/"uncontrollable" chronic problems

4 – Extremely severe/immediate treatment required/end organ failure/severe impairment of function

Adapted from [2]Extermann M, Overcash J, Lyman GH, Parr J, Balducci L, Comorbidity and functional status are independent in older patients. J Clin Oncol 1998; 16: 1582–87.

ORGAN SYSTEM	IF IMPAIRMENT, SPECIFY	SCORE
HEART		**0 1 2 3 4**
VASCULAR		**0 1 2 3 4**
HEMATOPOETIC		**0 1 2 3 4**
RESPIRATORY		**0 1 2 3 4**
ENT/LARYNX		**0 1 2 3 4**
UPPER GI		**0 1 2 3 4**
LOWER GI		**0 1 2 3 4**
LIVER		**0 1 2 3 4**
RENAL		**0 1 2 3 4**
GU		**0 1 2 3 4**
MUSCULOSKELETAL/INTEGUMENT		**0 1 2 3 4**
NEUROLOGICAL		**0 1 2 3 4**
ENDOCRINE/METABOLIC/BREAST		**0 1 2 3 4**
Calculated Ratings		
Total Number Categories Endorsed (this is the number of categories above that have a score >0)		
Total Score (this is the sum of the individual scores above)		
Severity Index (total score/total number of categories endorsed)		
Number of Categories at level 3 severity (this is the number of categories above that have a score of 3)		
Number of Categories at level 4 severity (this is the number of categories above that have a score of 4)		

Appendix I: Rai & Binet Staging

Rai Stage	Binet* Stage
0 Lymphocytes (L) in blood (>5000/µL)	**A** <3 sites involved, Hgb ≥10 g/dL, platelets ≥100,000/µL
I L + enlarged lymph nodes (LN)	
II L + spleen and/or liver (LN positive or negative)	**B** ≥3 sites involved, Hgb ≥10 g/dL, platelets ≥100,000/µL
III L + anemia (Hgb <11g/dL)	**C** Hgb <10 g/dL or platelets <100,000/µL
IV L + thrombocytopenia (platelets <100,000/µL)	

*Involved sites are liver, spleen, and lymph nodes in inguinal, auxiliary, and cervical regions.

Appendix J: New York Heart Association Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.
Class	**Objective Assessment**
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Appendix K: Definitions for PCYC-1112-CA Eligibility Criteria

Chemoimmuno-therapy	For the purpose of this protocol, a combination treatment regimen that contains both a cytotoxic, specifically a purine analog or alkylating agent, chemotherapy agent and an anti-CD20 monoclonal antibody (eg, rituximab) administered together.
Autoimmune hemolytic anemia (AIHA)	Defined by at least one marker of hemolysis (indirect bilirubin above the upper limit of normal (ULN) not due to liver disease, increased lactate dehydrogenase (above ULN) without alternative etiology, or increased absolute reticulocytosis (above ULN) or bone marrow erythropoiesis in the absence of bleeding) AND at least one marker of direct or indirect autoimmune mechanism (positive direct antiglobulin for IgG or C3d, cold agglutinins) (Ding 2007).
Immune thrombocytopenia (ITP)	Immune thrombocytopenia is defined by platelets ≤100,000/μL and increased megakaryocytes on the bone marrow exam.
Autoimmune cytopenia poorly responsive to therapy	Autoimmune anemia or thrombocytopenia poorly responsive to treatment includes those patients with recurrent autoimmune cytopenias, those receiving low dose steroids (≤ 20 mg of prednisone or equivalent) and those on intravenous immune globulin (IVIG). Patients receiving higher doses of steroids or experiencing declining platelets or hemoglobin due to autoimmune destruction during the 4 weeks prior to the first dose of study drug are considered for the purposes of this protocol to have uncontrolled autoimmune cytopenias (as defined below) and are not eligible for enrollment.
Autoimmune cytopenia, uncontrolled	Uncontrolled autoimmune anemia or thrombocytopenia is defined as those patients receiving > 20 mg prednisone (or equivalent) daily **or** have declining platelets or hemoglobin due to autoimmune destruction during the 4 weeks prior to the first dose of study drug.

Appendix L: Child-Pugh Score for Subjects with Liver Impairment

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

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

Source:

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

Appendix M: Schedule of Assessments for Patients Treated with Ofatumumab who are to Receive Next-line Ibrutinib Therapy

Study Weeks	Assessment for Next-line Ibrutinib Therapy	Treatment Phase			Follow-up Phase
		Every 4 weeks for 24 weeks	Every 12 weeks until PD	End-of-Treatment Visit	Follow-up (Every 12 weeks)
Study Windows	±14 d	±7 d	±7 d	30 (±3 d)	±7 d
Study Drug Administration					
Ibrutinib 420 mg per day PO		Continuous Daily Dosing			
Procedures					
Medical Monitor approval	X				
Concomitant medications	X	X	X	X	
Adverse events		X	X	X	
Physical examination, vital signs, ECOG	X	X	X	X	
Hematology	X	X[e]	X	X	
Serum chemistry	X				
PK sampling if on CYP3A4/5 inhibitors [d]					
Disease assessment:					
Investigator assessment of response and for progression[a]			X		
Predictive biomarkers			X[b]		
Survival status					X[c]
Subsequent anticancer therapies					X[c]

CLL=chronic lymphocytic leukemia; d=day; ECOG=Eastern Cooperative Oncology Group; IRC=Independent Review Committee; PD=progressive disease; PO=oral; qd=once daily

a. Efficacy assessments should include CT scan annually until the first disease progression on protocol. For patients who have had experienced PD and are crossed over to ibrutinib, CT scans for response assessments may be performed at investigator's discretion.

b. Blood samples will be collected at Week 12 Day 1 and at PD

c. By telephone

d. Patients who must take strong or moderate CYP3A4/5 inhibitors while on treatment with ibrutinib, additional PK collections for evaluation of ibrutinib exposure is requested at the following scheduled visit after concomitant CYP3A4/5 inhibitor has started and still in use. Please refer to Section 7.1.21 for the PK collection schedules.

e. CBC should be performed weekly for the first 4 weeks