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PROTOCOL

TITLE:	An Open-label Extension Study in Patients 65 Years or Older with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib versus Chlorambucil)
PROTOCOL NUMBER:	PCYC-1116-CA
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
EUDRACT NUMBER	2012-003968-44
SPONSOR MEDICAL MONITOR:	[redacted] MD Phone: [redacted]
SPONSOR:	Pharmacyclics LLC 1000 Gateway Boulevard South San Francisco, CA 94080 United States of America
ORIGINAL PROTOCOL DATE:	28 September 2012
AMENDMENT 1 DATE:	28 May 2014
AMENDMENT 2 DATE:	19 October 2016
AMENDMENT 3 DATE:	12 July 2018
AMENDMENT 4 DATE:	10 October 2022

Confidentiality Statement

PROTOCOL APPROVAL PAGE

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I have carefully read Protocol PCYC-1116-CA Amendment 4 entitled "An Open-label Extension Study in Patients 65 Years or Older with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib versus Chlorambucil)." 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 LLC, 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 LLC. All data pertaining to this study will be provided to Pharmacyclics LLC. The policy of Pharmacyclics LLC, requires that any presentation or publication of study data by clinical investigators be reviewed by Pharmacyclics LLC, 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:

[redacted] 15-Nov-2022

Medical Monitor's Signature Date

[redacted] MD
Clinical Science, Pharmacyclics LLC

SYNOPSIS

Title	An Open-label Extension Study in Patients 65 Years or Older with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib versus Chlorambucil)
Protocol Number	PCYC-1116-CA
Study Phase	3
Study Duration	Approximately 10 years from randomization of the first patient in the parent study (ie, Study PCYC-1115-CA).
Investigational Product	Ibrutinib oral (PO) hard gelatin capsule
Reference Therapy	None
Objectives	• To monitor progression-free survival (PFS) • To continue treatment and safety assessment of patients randomized to Arm B (ibrutinib) in Study PCYC-1115-CA (the parent study) who have not progressed at the time of parent study closure • To follow patients for long-term outcome • To capture overall response rate (ORR), duration of response (DOR), PFS, and overall survival (OS), and time to next therapy • To fulfill long-term follow-up requirements of randomized patients after closure of the parent study, including OS

Study Design	Study PCYC-1116-CA is an open-label, multicenter extension of Study PCYC-1115-CA (the parent study), and it will run concurrently with the parent study. A patient will be transferred to PCYC-1116-CA after Independent Review Committee (IRC) confirmation of disease progression (PD) in the parent study or at closure of the parent study by the Sponsor, whichever comes first. After PD, selection of second-line therapy, when clinically indicated, is at the discretion of the investigator and can include second-line ibrutinib (for patients randomized to chlorambucil in the parent study who also meet the criteria for second-line ibrutinib therapy [Section 4.2][‡]) second-line chlorambucil (for patients randomized to ibrutinib in the parent study), or other therapies. Transfer of patients from the parent study and treatment in the extension study are described in Table 1. Assessments in the extension study vary depending on the treatment to which the patient was randomized in the parent study, the disease-progression status

[‡] **Note: second-line ibrutinib is not applicable after implementation of Protocol Amendment 3.**

	at transfer to the extension study, and the planned treatment in the extension study; assessments are summarized in the schedules of assessments (Appendix A, Appendix B, Appendix C and Appendix D). Patients will be followed for long-term outcome, including PFS, OS, ORR, and when applicable, response to next treatment. **After Implementation of Protocol Amendment 3:** • Patients randomized to chlorambucil who have not progressed on the study and have not started subsequent anticancer therapy, and patients randomized to ibrutinib will be followed on the study. • Patients randomized to chlorambucil who progressed will exit the study. • Second-line ibrutinib patients will be given the opportunity to enroll into a separate long-term ibrutinib extension study if they meet the eligibility criteria of that study.
Population	This study will enroll patients 65 years or older with CLL or SLL who previously participated in the parent study.
Centers	Multicenter, multinational
Eligibility Criteria for PCYC-1116-CA	To enroll in Study PCYC-1116-CA, patients must meet all of the following criteria: 1. Randomized in the parent study, PCYC-1115-CA 2. Informed consent for Study PCYC-1116-CA 3. IRC-confirmed PD in the parent study or closure of the parent study
Additional Criteria for Receiving Second-line Ibrutinib‡ (Second-line ibrutinib will no longer be initiated following implementation of Protocol Amendment 3)	To receive second-line ibrutinib, patients must meet all of the following criteria: 1. IRC-confirmed disease progression in the parent study (PCYC-1115-CA), or for patients who did not progress in the parent study, investigator-determined disease progression in the extension study (PCYC-1116-CA) 2. Received at least 3 cycles of chlorambucil therapy 3. Documented, protocol-defined reason for chlorambucil discontinuation: • No evidence of response in radiographically assessed disease parameters at Cycle 5 compared to baseline; no further response (defined as failure to reach at least a PR, or a plateau of response with no further improvement of disease parameters) after at least 6 cycles; could not tolerate treatment (a situation defined by the recurrence of toxicity of at least Grade 3 despite appropriate dose reductions and optimal symptomatic management); or maximum treatment of 12 cycles with chlorambucil 4. Demonstrates continuation of adequate organ function, performance status, and other criteria, as follows: • Eastern Cooperative Oncology Group (ECOG) status of 0-2 • Adequate hematologic function, defined as ANC $\geq 0.75 \times 10^9$/L (independent of growth factor support in the preceding 7 days) and platelet count $\geq 30 \times 10^9$/L (independent of transfusion or growth factor support in the preceding 7 days)

	• Adequate hepatic function, defined as serum aspartate transaminase (AST) and alanine transaminase (ALT) < 2.5 x upper limit of normal (ULN), and total bilirubin ≤ 1.5 x ULN (unless due to Gilbert's syndrome) • Adequate renal function, defined as an estimated glomerular filtration rate ≥ 30 mL/min using the Cockcroft-Gault equation • Patients must have recovered from acute toxicities due to prior chemotherapy, radiotherapy, investigational drugs or experimental treatments (non-hematologic toxicities have resolved to a NCI CTCAE [version 4.03] Grade of ≤2) prior to receiving next line ibrutinib on this study 5. Meets at least 1 of the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria for active disease requiring treatment (Hallek 2008): • Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/μL) • Massive (≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly • Massive nodes (at least 10 cm longest diameter), progressive, or symptomatic lymphadenopathy • Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of < 6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of < 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. • Autoimmune hemolytic anemia and/or immune thrombocytopenia (see definitions below) that is poorly responsive to corticosteroids or other standard therapy (Definitions: Autoimmune hemolytic anemia is defined by at least 1 marker of hemolysis [indirect bilirubin above the 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 1 marker of direct or indirect autoimmune mechanism [positive direct antiglobulin for IgG or C3d, cold agglutinins] [Ding 2007]. Autoimmune thrombocytopenia is defined by platelets ≤100,000/μL and increased megakaryocytes on the bone marrow examination.) • Constitutional symptoms, defined as 1 or more of the following disease-related symptoms or signs, documented in the patient's record prior to randomization:

	– Unintentional weight loss > 10% within 6 months prior to Screening – Significant fatigue (inability to work or perform usual activities) – Fevers > 100.5°F or 38.0°C for 2 or more weeks prior to Screening without evidence of infection – Night sweats for more than 1 month prior to Screening without evidence of infection 6. Obtained the Sponsor's approval for second-line ibrutinib therapy **To receive second-line ibrutinib, patients must meet NONE of the following criteria:** 1. Disease progression involving the central nervous system (CNS) or transformation to another histology 2. Intervening chemotherapy, immunotherapy, or investigational agent specifically to treat CLL if administered before date of IRC confirmed progressive disease 3. In the 4 weeks before dosing: radiation therapy, major surgery, or receipt of an investigational drug 4. Requirement for treatment with a strong CYP3A inhibitor 5. Uncontrolled systemic infection or requirement for IV antibiotics 6. Noncompliance on the parent study
Endpoints	The endpoints of PCYC-1116-CA are as follows: • PFS on first-line therapy • PFS after initiation of subsequent anticancer therapy (PFS2) • Overall survival • Time to next treatment • ORR and DOR • Safety as measured by all AEs and serious adverse events (SAEs) • Disease outcome following cessation of ibrutinib therapy after attainment of minimal residual disease (MRD)-negative remission in those patients receiving ibrutinib as second-line therapy
Transfer from Parent Study to PCYC-1116-CA	Patients are transferred from the parent study to this extension study as described in Table 1.
Study Treatment in PCYC-1116-CA	The treatment options in this extension study are described below.
Ongoing ibrutinib (first-line therapy)	Patients who received ibrutinib in the parent study and have not progressed at the time of parent study closure will be transferred to Study PCYC-1116-CA to continue on their current tolerated dose of ibrutinib. Treatment will continue until PD, unacceptable toxicity, start of subsequent anticancer therapy or other reason for treatment discontinuation.

Alternative anticancer treatment (second-line therapy)	At the investigator's discretion, alternative anticancer treatment is a therapeutic option for patients who experience PD during ibrutinib therapy or during or after chlorambucil treatment. Alternative treatment can also be considered if drug is discontinued for other reasons (eg, intolerability or adverse event [AE]). Selection of the drug(s) and treatment regimen(s) is at the investigator's discretion. For patients randomized to ibrutinib in the parent study, chlorambucil can be used for second-line therapy. Second-line ibrutinib therapy‡ is a treatment option for those patients who experience PD during or after chlorambucil treatment and meet criteria for chlorambucil discontinuation in the parent study. The patients must meet the criteria described above (in "Additional Criteria for Receiving Second-line ibrutinib"). Ibrutinib dosing is initiated at 420 mg (3 x 140-mg capsules), orally, once daily. If necessary, the dose can be decreased as described in this protocol. At the investigator's discretion, patients receiving second-line ibrutinib therapy‡ who achieve and retain MRD-negative remission for 6 cycles (including 2 sequential MRD-negative assessments at least 2 cycles apart that include at least one bone marrow aspirate) can have their ibrutinib discontinued. If second-line ibrutinib is discontinued, the patient will be followed for MRD recurrence by peripheral blood monitoring approximately every 6 cycles; ibrutinib therapy may be reinitiated in the event of recurrence of MRD positive status or clinical progression.
No anticancer treatment	Patients can elect to forego further anticancer therapy, or patients may not have met IWCLL criteria for active disease requiring anticancer therapy.
Safety Plan:	A Pharmacovigilance Committee will compare adverse events in the study with safety data from the entire clinical trial database for ibrutinib. 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).

Statistical Methods	All statistics will be descriptive; no inferential hypothetical tests will be conducted. Each efficacy endpoint will be descriptively analyzed based on combined data from the parent study and Study PCYC-1116-CA as appropriate. A descriptive update of PFS on the original randomized therapy will be conducted at the close of Study PCYC-1116-CA, along with OS. Medians for PFS and OS and their 95% confidence intervals will be estimated using the Kaplan-Meier method for all patients randomized in Study PCYC-1115-CA. The overall response rate will be described by crude proportion of patients achieving a complete response (CR) or partial response (PR). For patients receiving second-line ibrutinib who achieve MRD-negative remission, crude proportion, duration of MRD negativity, and the proportion of patients who recur after cessation of treatment will be calculated. Verbatim descriptions of AEs will be coded to a preferred term and mapped to System Organ Class using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs that started during treatment and up to 30 days after the last dose of study drug are considered treatment-emergent and will be tabulated.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CERT	Center for Education and Research on Therapeutics
CFR	Code of Federal Regulations
cGVHD	chronic graft versus host disease
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete remission (response)
CRF	case report form
CRi	CR with incomplete bone marrow recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
del 17p	deletion of the short arm of chromosome 17
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMR	electronic medical records
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FACiT-F	The Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration (United States)
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	investigator's brochure
IC_{50}	half maximal inhibitor concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	interstitial lung disease

Abbreviation	Definition
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
ITT	intent to treat
IV	Intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDH	lactate dehydrogenase
LDT	lymphocyte doubling time
LN	lymph node
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
nPR	nodular partial remission (response)
ORR	Overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
QTc	corrected QT interval
REB	Research Ethics Board
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SCARs	severe cutaneous adverse reactions
SEER	Surveillance Epidemiology and End Results
SJS	Stevens-Johnson syndrome
SLL	small lymphocytic lymphoma
SOP	standard operating procedure
SPD	sum of the products of diameters
TLS	tumor lysis syndrome
TN	treatment naive
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

1.1. Ibrutinib Overview

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development LLC (collectively referred to as the Sponsor) for the treatment of B-cell malignancies.

Ibrutinib has been approved in many regions, including the United States (US) and European Union (EU), for indications including treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) including CLL/SLL with a deletion of the short arm of chromosome 17 (del17p), patients with Waldenström's macroglobulinemia, patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy, and for patients with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

For the most up to date and 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 and/or the applicable regional labeling information.

1.2. Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

CLL is the most common form of adult leukemia in the developed world. The estimated 2010 prevalence in the United States (US) was approximately 106,000 individuals (SEER 2010). The median age at presentation is typically between 65 and 68 years; a population-based study found that more than half of the cases presented at over 70 years of age (Brenner 2008). CLL is characterized by an accumulation of monoclonal mature B cells ($CD5^+/CD23^+$) in the blood, bone marrow, and secondary lymph organs. These cells are constantly being stimulated by their BCR, as well as by interactions with their microenvironment (Chiorazzi 2005). According to the World Health Organization (WHO), SLL, a disease with similar pathological findings but without the lymphocytosis, is considered to be a manifestation of the same underlying disorder as CLL (Campo 2011).

Once diagnosed with CLL or SLL, patients can have a variable course—some not requiring treatment for more than a decade and others requiring more urgent treatment, particularly those with clinically symptomatic disease (Gribben 2011). According to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines, the following features are indications for therapy: progressive marrow failure (manifested by anemia or thrombocytopenia), massive or progressive splenomegaly (6 cm or greater), massive lymph nodes (10 cm or greater in the longest diameter), progressive lymphocytosis with a rapid lymphocyte doubling time occurring in less than 6 months, worsening autoimmune cytopenias resistant to corticosteroids or other standard treatment, and constitutional symptoms (Hallek 2008).

1.3. Standard Treatment and Unmet Medical Need

The past decade has seen significant advancement in the treatment of CLL. A number of new agents have been evaluated and approved for the treatment of patients with CLL, such as alemtuzumab, bendamustine, ofatumumab, and rituximab. Chemo-immunotherapy regimens containing a nucleoside analog and an anti-CD20 agent have markedly improved outcomes when used as initial therapy in young otherwise healthy patients requiring treatment.

The choice of treatment and its intensity at any particular point in the management of this disease is largely dependent upon patient age, comorbidities, ability to tolerate treatment, presence of poor-risk molecular features, cumulative toxicities, and in salvage therapy, the duration of the response to prior therapy. Historically, the main front-line treatment for CLL was chlorambucil. Over the past 2 decades, however, newer agents and combinations of chemotherapy have been shown to be superior to chlorambucil, but these studies have largely excluded elderly patients. Fludarabine, bendamustine, and alemtuzumab as single agents have shown improved efficacy compared with chlorambucil when evaluated in patients with a median age of less than 65 years (Rai 2000; Hillmen 2007; Cheson 2009; Knauf 2009). However, in the only Phase 3 study comparing fludarabine with chlorambucil in a randomized fashion in CLL patients 65 years or older (Eichhorst 2009), there was no benefit in progression-free survival (PFS) (18 versus 19 months, respectively) or in overall survival (OS) (46 versus 64 months, respectively).

The addition of cyclophosphamide to fludarabine further improved response rates and PFS compared with fludarabine alone, but at the cost of increased toxicity (Flinn 2000, O'Brien 2001, Eichhorst 2006; Flinn 2007). In a large Phase 3 clinical trial for the first-line treatment of CLL, the addition of rituximab, an anti-CD20 monoclonal antibody, to fludarabine and cyclophosphamide in the front-line setting resulted in significant improvement in PFS and OS compared with fludarabine and cyclophosphamide alone, with a hazard ratio for progression of 0.51 (95% CI: 0.39, 0.67) for patients less than 70 years of age (N=736) (Hallek 2010; Casak 2011). However, the treatment effect in patients 70 years or older (N=81) was decreased, with a hazard ratio of 1.17 (95% CI: 0.51, 2.66). This trend of diminished efficacy (PFS hazard ratio > 1.00) was also seen in patients 70 years or older in a second-line study comparing the same combination regimens (Robak 2010). Elderly patients experienced greater toxicity than younger patients in general and with rituximab—particularly cytopenias (Casak 2011).

Thus, despite these advances, additional treatment options are desirable—especially in the elderly population in which tolerance to chemotherapeutic agents can be a challenge.

1.4. Summary of Nonclinical Data

1.4.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the BTK (Pan 2007). In vitro, ibrutinib is a potent inhibitor of BTK activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position.

When added directly to human whole blood, ibrutinib inhibits signal transduction from the 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).

For more detailed and comprehensive information regarding nonclinical pharmacology, please refer to the current IB.

1.4.2. 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 (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.

For the most up to date and comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current IB.

1.5. Summary of Clinical Data

For the most up to date and comprehensive clinical information regarding ibrutinib, please refer to the current version of the IB.

1.5.1. 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 inter-subject 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.

1.5.2. Summary of Clinical Safety

A brief summary of safety data from monotherapy studies is provided below. For the most recent and the 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).

1.5.2.1. Monotherapy Studies

Integrated safety data are shown for 1,523 subjects with B-cell malignancies treated with ibrutinib monotherapy in 17 studies that have completed primary analysis or final analysis as of the 31 July 2017 cutoff date for the version 11 Investigator's Brochure update.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N = 1,523):

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

[a] Table 5 of ibrutinib IB; [b] Table 6 of ibrutinib IB.

1.5.3. Risks

1.5.3.1. Bleeding-related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, subdural intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 5.5.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 5.6 for guidance on ibrutinib management with surgeries or procedures.

1.5.3.2. Cardiac Arrhythmias and Cardiac Failure

Atrial fibrillation, atrial flutter, cardiac failure and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persists, consider the risks and benefits of ibrutinib therapy, and follow the protocol dose modification guidelines (see Section 5.2.3).

1.5.3.3. Rash

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

agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.5.3.4. Non-melanoma skin cancer

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

1.5.3.5. 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) and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

1.5.3.6. 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.

1.5.3.7. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. Should symptoms develop, follow the protocol dose modification guidelines (see Section 5.2.3).

1.5.3.8. 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.

1.5.3.9. 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 5.2.3).

1.5.3.10. 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.

1.5.3.11. 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 5.2.3.

1.5.3.12. Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/µL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis (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 8.0 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL. This pharmacodynamic effect was less prominent or not observed in other indications.

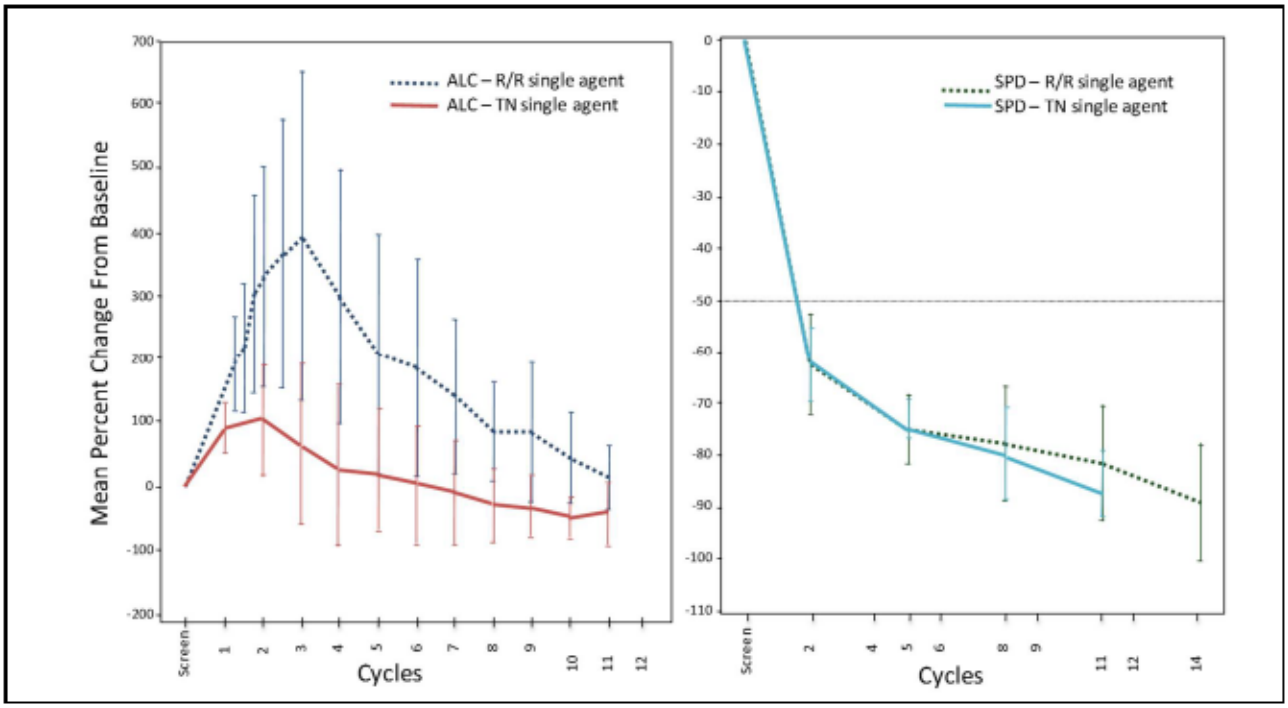
For subject and ibrutinib management guidance, refer to Section 5.2.4.

1.5.4. 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 3 major effects: (1) direct induction of apoptosis, (2) inhibition of cell homing and migration to chemokines 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 2011; 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 1).

Figure 1: Changes in Peripheral Blood Lymphocyte Counts and Burden of Lymphadenopathy in Patients with CLL/SLL, Study PCYC-1102-CA



ALC=absolute lymphocyte count; R/R= relapsed/refractory; SPD=sum of products of lymph node dimension; TN=treatment naive

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 therapy (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 2016 guideline and the clarification of the IWCLL 2008 criteria by its authors (Hallek 2012).

1.6. Rationale for Trial

Ibrutinib has demonstrated promising activity in studies enrolling older patients with treatment-naive or relapsed/refractory CLL and older patients with SLL. The parent study, PCYC-1115-CA, evaluates ibrutinib in treatment-naive elderly patients with CLL or SLL. This open-label extension study provides options for continued treatment and follow-up of patients randomized in the parent study.

Modeled after the design of the pivotal study of imatinib, IRIS, in chronic phase CML (O'Brien 2003), patients in PCYC-1116-CA will be allowed to receive the investigator's choice of second-line therapy if clinically indicated and IRC PD has been confirmed, including an option for ibrutinib for relapsed CLL/SLL patients. Patients aged 65 or older who experience progression within 12 months of last dose of chlorambucil have a higher risk of early death compared to those with longer remissions (Catovsky 2007). Patients who have acquired a deletion of the short chromosome of 17 (del 17p) during or following treatment with chlorambucil would also not be considered appropriate for fludarabine or alkylating based therapy. In these high-risk populations, the use of investigational agents is justified due to the paucity of data to support safe and effective commercially available therapies in the relapsed elderly or frail CLL patients, either with monotherapy (Hillmen 2007, Eichhorst 2009, Knauf 2009) or with combination therapies (Casak 2011, Fischer 2011). In CLL patients with del 17p, effective treatment options are even more limited; alemtuzumab has demonstrated efficacy, but the safety profile with severe cytopenias and infectious complications has precluded its safe use in the elderly population (Lozanski 2004).

2. STUDY OBJECTIVES

- To monitor PFS
- To continue treatment and safety assessment of patients randomized to Arm B (ibrutinib) in Study PCYC-1115-CA (the parent study) who have not progressed at the time of parent study closure
- To follow patients for long-term outcome
- To capture overall response rate (ORR), duration of response (DOR), PFS, and OS, and time to next therapy
- To fulfill long-term follow-up requirements of randomized patients after closure of the parent study, including OS

3. STUDY DESIGN

This open-label extension study provides ongoing treatment and follow-up for elderly patients with CLL or SLL who were previously enrolled in the parent study, PCYC-1115-CA. Patients who were randomized in the parent study are transferred to this extension study when they experience independent review committee (IRC)-confirmed progressive disease (PD) or when the parent study is closed by the Sponsor, as described in Table 1.

Table 1: Patient Transfer to Study PCYC-1116-CA and Assessments within PCYC-1116-CA

Status at Transfer from Parent Study, PCYC-1115-CA		Assessments After Transfer to Extension Study, PCYC-1116-CA
PCYC-1115-CA Arm A or B Patients: IRC-confirmed PD in parent study	→	Schedule of assessments is based on management decision: • No therapy: See Appendix D • Second-line ibrutinib (if eligible)‡: See Appendix C • Second-line non-ibrutinib therapy: See Appendix D
PCYC-1115-CA Arm A Patients: Completion of 12 cycles of chlorambucil, and no PD at closure of parent study OR Discontinuation of randomized treatment for a reason other than PD, and no PD at closure of the parent study	→	Before PD, schedule of assessments is in Appendix A; After PD, schedule of assessments is based on management decision: • No therapy: See Appendix D • Second-line ibrutinib (if eligible)‡: See Appendix C • Second-line non-ibrutinib therapy: See Appendix D
PCYC-1115-CA Arm B Patients: Ongoing treatment with ibrutinib, and no PD at closure of parent study OR Discontinuation of randomized treatment for a reason other than PD, and no PD at closure of the parent study	→	Before PD, schedule of assessments is in Appendix B; After PD, schedule of assessments is as follows: • No therapy: See Appendix D • Second-line non-ibrutinib therapy: See Appendix D

Arm A=chlorambucil in PCYC-1115-CA; Arm B=ibrutinib in PCYC-1115-CA; IRC=Independent Review Committee; non-ibrutinib =alternative anticancer treatment other than ibrutinib; PD=progressive disease

Note: Alternative anticancer treatment is selected at the investigator's discretion. For a patient randomized to chlorambucil in the parent study, ibrutinib is an option for second-line therapy, provided the patient meets the criteria for second-line ibrutinib therapy (Section 4.2)‡. For a patient randomized to ibrutinib in the parent study, chlorambucil is an option for second-line therapy.

Treatment options in this extension study vary depending on the treatment to which the patient was randomized in the parent study, the disease-progression status at transfer to the extension study, and the planned treatment in the extension study. Choice of second-line alternative anticancer treatment is at the clinical judgment of the investigator. Treatment can be with ibrutinib (for patients randomized to chlorambucil in the parent study who fulfill the criteria for second-line ibrutinib [Section 4.2]‡), chlorambucil (for patients randomized to ibrutinib in the parent study), or other therapies. In addition, any patient can elect not to undergo further anticancer treatment.

After Implementation of Protocol Amendment 3 (Table 2):

Patients randomized to first-line chlorambucil or ibrutinib, who have not progressed and did not receive subsequent anticancer therapy, will continue their participation in the study.

Patients randomized to first-line chlorambucil once progressed post their first-line therapy will exit the study and the initiation of second-line treatment with ibrutinib will not be available for these patients on Study PCYC-1116-CA. Note, with the implementation of Amendment 3, first-line chlorambucil patients, who have withdrawn partial consent and are being followed up for overall survival only, will also exit the study.

Patients randomized to first-line ibrutinib who have withdrawn partial consent and are being followed up for overall survival only will continue their participation in the study.

Patients randomized to first-line chlorambucil who are receiving ibrutinib on study will exit and will be given the opportunity to enroll into a separate long-term ibrutinib extension study if they meet the eligibility criteria of that study or can continue therapy from commercial source.

Patients who were randomized to ibrutinib and have progressed will continue to be followed in the study.

Table 2: Patient Handling after Implementation of Protocol Amendment 3

Protocol Amendment # 2	**Protocol Amendment # 3**
Subject is in Appendix A (randomized to **first-line chlorambucil)** and has not progressed and did not receive subsequent anticancer therapy	Continue on study to follow for PFS and then exit
Subject is in Appendix B (randomized to **first-line ibrutinib)** and has not progressed and did not receive subsequent anticancer therapy	Continue on study to follow for PFS, then transfer to Appendix D until study is closed
Subject is in Appendix C **(second-line ibrutinib)**	Exit the study with option to roll-over to another long-term ibrutinib study, if eligible
Subject is in Appendix D: • Randomized to chlorambucil	Exit study
• Randomized to ibrutinib	Continue on study to follow for OS until study is closed

Dosing in this study is as follows:

- Patients continuing on first-line ibrutinib therapy enter this study at their current tolerated dose. Dose adjustment, if required, is described in Section 5.2.3.
- Patients initiating second-line ibrutinib therapy‡ start treatment at a dose of 420 mg/day. Dose reduction, if required is described in Section 5.2.3.
- The dose(s) and treatment regimen(s) for other alternative anticancer treatment— which could be chlorambucil, for patients initially randomized to ibrutinib— is selected by the investigator in light of the current standard of care.

Patients receiving first-line or second-line ibrutinib therapy‡ in the extension study will be followed for safety, response (including disease progression), and survival. Assessments in specific subgroups of patients are described in detail in the schedules of assessments: Appendix A, assessments before PD in patients randomized to chlorambucil; Appendix B, assessments before PD in patients randomized to ibrutinib; Appendix C, assessments after PD in patients on second-line ibrutinib‡; and Appendix D, assessments after PD in patients on anticancer treatment other than ibrutinib (ie, non-ibrutinib), or no treatment.

Unlike the parent study, in this extension study, PD is established by the investigator; there is no confirmation of PD by an IRC.

At the investigator's discretion, patients receiving second-line ibrutinib therapy‡ who achieve and retain MRD-negative remission for 6 cycles (including 2 sequential MRD-negative assessments at least 2 cycles apart that include at least one bone marrow aspirate) can have their ibrutinib discontinued. If second-line ibrutinib is discontinued, the subject will be followed for MRD recurrence by peripheral blood monitoring approximately every 6 cycles; ibrutinib therapy may be reinitiated in the event of recurrence of MRD positive status or clinical progression.

Following implementation of Protocol Amendment 3, re-initiation of ibrutinib therapy will no longer be permitted as part of the PCYC-1116-CA Study. Such therapy can only be done with commercial drug supply or as part of the separate long-term ibrutinib extension study if a subject meets the eligibility criteria.

3.1. Criteria for Transfer to This Extension Study

Patients who demonstrate IRC-confirmed disease progression in the parent study (either on randomized treatment or during follow-up) will complete an end-of-treatment visit up to 30 days after treatment discontinuation and will then be transferred to the extension study, PCYC-1116-CA.

If treatment is discontinued in the absence of IRC-confirmed progression (ie, for an AE, or withdrawal from treatment by the patient or investigator's decision), patients will remain in the parent study to monitor for first progression.

Any patient who withdraws consent from Study PCYC-1115-CA will be ineligible for the extension study.

At the time of parent study closure, all remaining patients will be transferred to the extension study for continued follow-up.

Second-line treatment, if clinically indicated, will be at the investigator's discretion. Arm A patients (ie, randomized to chlorambucil) who progress and wish to initiate second-line treatment with ibrutinib in the extension study must meet all specific criteria in Section 4.2‡.

4. SELECTION OF PATIENTS

This study is designed to enroll patients who were randomized in the parent Study PCYC-1115-CA.

4.1. Eligibility Criteria

To enroll in Study PCYC-1116-CA, patients must meet all of the following criteria:

1. Randomized in the parent study, PCYC-1115-CA
2. Informed consent for Study PCYC-1116-CA
3. IRC-confirmed PD in the parent study or closure of the parent study

4.2. Additional Criteria for Receiving Second-line Ibrutinib‡

(Note: second-line treatment with ibrutinib will no longer be initiated following implementation of Protocol Amendment 3)

To receive second-line ibrutinib, patients must meet all of the following criteria:

1. IRC-confirmed disease progression in the parent study (PCYC-1115-CA), or for patients who did not progress in the parent study, investigator-determined disease progression in the extension study (PCYC-1116-CA)
2. Received at least 3 cycles of chlorambucil therapy
3. Documented, protocol-defined reason for chlorambucil discontinuation:
   - No evidence of response in radiographically assessed disease parameters at Cycle 5 compared to baseline; no further response (defined as failure to reach at least a PR, or a plateau of response with no further improvement of disease parameters) after at least 6 cycles; could not tolerate treatment (a situation defined by the recurrence of toxicity of at least Grade 3 despite appropriate dose reductions and optimal symptomatic management); or maximum treatment of 12 cycles with chlorambucil
4. Demonstrates continuation of adequate organ function, performance status, and other criteria, as follows:
   - Eastern Cooperative Oncology Group (ECOG) status of 0-2
   - Adequate hematologic function, defined as absolute neutrophil count (ANC) $\geq 0.75 \times 10^9$/L (independent of growth factor support in the preceding 7 days) and platelet count

≥ 30 x 10^9/L (independent of transfusion or growth factor support in the preceding 7 days)

- Adequate hepatic function, defined as serum aspartate transaminase (AST) and alanine transaminase (ALT) < 2.5 x upper limit of normal (ULN), and total bilirubin ≤ 1.5 x ULN (unless due to Gilbert's syndrome)
- Adequate renal function, defined as an estimated glomerular filtration rate ≥ 30 mL/min using the Cockcroft-Gault equation
- Patients must have recovered from acute toxicities due to prior chemotherapy, radiotherapy, investigational drugs or experimental treatments (non-hematologic toxicities have resolved to a NCI CTCAE [version 4.03] Grade of ≤2) prior to receiving next line ibrutinib on this study

5. Meets at least 1 of the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria for active disease requiring treatment (Hallek 2008):
   - Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (hemoglobin < 10 g/dL), and/or thrombocytopenia (platelets < 100,000/μL)
   - Massive (≥ 6 cm below the left costal margin), progressive, or symptomatic splenomegaly
   - Massive nodes (at least 10 cm longest diameter), progressive, or symptomatic lymphadenopathy
   - Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of < 6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of < 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.
   - Autoimmune hemolytic anemia and/or immune thrombocytopenia (see definitions below) that is poorly responsive to corticosteroids or other standard therapy.
     (Definitions: Autoimmune hemolytic anemia is defined by at least 1 marker of hemolysis [indirect bilirubin above the 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 1 marker of direct or indirect autoimmune mechanism [positive direct antiglobulin for IgG or C3d, cold agglutinins] [Ding 2007]. Autoimmune thrombocytopenia is defined by platelets ≤ 100,000/μL and increased megakaryocytes on the bone marrow examination.)
   - Constitutional symptoms, defined as 1 or more of the following disease-related symptoms or signs, documented in the patient's record prior to randomization:
     - Unintentional weight loss > 10% within 6 months prior to Screening
     - Significant fatigue (inability to work or perform usual activities)
     - Fevers > 100.5°F or 38.0°C for 2 or more weeks prior to Screening without evidence of infection

- Night sweats for more than 1 month prior to Screening without evidence of infection

6. Obtained the Sponsor's approval for second-line ibrutinib treatment.

To receive second-line ibrutinib, patients must not meet any of the following criteria:

1. Disease progression involving the central nervous system (CNS) or transformation to another histology
2. Intervening chemotherapy, immunotherapy, or investigational agent specifically to treat CLL if administered before date of IRC confirmed progressive disease
3. In the 4 weeks before dosing, radiation therapy, major surgery, or receipt of an investigational drug
4. Requirement for treatment with a strong CYP3A inhibitor
5. Uncontrolled systemic infection or requirement for intravenous (IV) antibiotics
6. Noncompliance on the parent study

5. TREATMENTS

Before implementation of Amendment No. 3:

Choice of second-line alternative anticancer treatment is at the clinical judgment of the investigator. Second-line treatment can include ibrutinib (for patients randomized to chlorambucil in the parent study who fulfill the criteria for second-line ibrutinib [Section 4.2‡], chlorambucil (for patients randomized to ibrutinib in the parent study), or other therapies. In addition, any patient can elect not to undergo further anticancer treatment.

After implementation of Amendment No. 3:

Patients randomized to chlorambucil will be followed until progression. Following progression, these subjects will exit the study and the initiation of second-line treatment with ibrutinib will not be available for these patients on Study PCYC-1116-CA.

Patients randomized to first-line ibrutinib will continue to receive ibrutinib until progression.

In order to minimize or avoid treatment interruptions, patients on second-line ibrutinib opting to move to another long-term extension study, may be allowed to continue treatment within this study for a limited time before transitioning to the other study.

5.1. Identification of Alternative Anticancer Treatments

5.1.1. Ibrutinib

Ibrutinib is supplied as hard gelatin capsules, each of which contains 140 mg of ibrutinib. The capsules are packaged in opaque high-density polyethylene 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. Refer to the pharmacy binder and study drug label for more detailed information.

Refer to the ibrutinib IB for additional information regarding the drug product.

5.1.2. Non-ibrutinib Therapies

Specific agent(s) and the treatment regimen(s) are selected per the clinical judgment of the investigator. For drug therapies, refer to the package insert.

5.1.3. No Treatment

A patient can elect not to receive further anticancer treatment.

5.2. Ibrutinib

5.2.1. Dosage and Administration

Patients continuing on first-line ibrutinib therapy enter this study at their current tolerated dose, while those initiating second-line ibrutinib therapy‡ start treatment at an oral dose of 420 mg/day (3 x 140-mg capsules).

Ibrutinib is 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 least 30 minutes before eating or at least 2 hours after a meal, at approximately the same time each day. The use of strong CYP3A inhibitors/inducers and grapefruit and Seville oranges (due to CYP3A inhibition) should be avoided for the duration of the study (Appendix G).

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

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Study drug may not be shipped to the subject without approval from PCYC and may not be dispensed to anyone other than the subject. Ibrutinib will be dispensed to patients in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 11.8) updated at each visit. Returned capsules must not be re-dispensed to anyone.

Dose modifications for toxicity are described below in Section 5.2.3.

5.2.2. 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 8.3 for further information regarding AE reporting.

5.2.3. Dose Hold, Reduction, or Discontinuation

Treatment with ibrutinib must be held for any unmanageable, potentially study drug-related toxicity that is Grade 3 or higher in severity. Please see Section 5.5.3 for guidance for management of ibrutinib in patients who require anticoagulant treatment.

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.

A hematologic AE grading scheme for hematologic toxicity is included in Appendix I.

The actions in Table 3, and Table 4 should be taken for the following toxicities:

- Grade 3 or greater neutropenia with infection or fever
- Grade 4 neutropenia (ANC < 500/μL) for > 7 days (Neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines [Smith 2006] and use must be recorded in the case report form [CRF].)
- Grade 3 or 4 thrombocytopenia (platelets< 50,000/μL); or, in patients with baseline thrombocytopenia, a platelet decrease of 50%-74% from baseline in presence of bleeding
- Grade 4 thrombocytopenia (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 greater non-hematological toxicity (Note: Table 4 recommendations for Grade 3 or higher cardiac failure and cardiac arrhythmias)
- Grade 2 cardiac failure (Table 4)
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity

For other AEs, including grade 2 AEs, that are deemed per the investigator potentially manageable by dose reduction, these can be managed with a one dose level dose reduction.

Table 3: Drug Discontinuation Actions for Ibrutinib for Events not Specified in Table 4.

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

[a] 1st, 2nd, 3rd, or 4th occurrence of the *same* toxicity

[b] When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg.

Table 4: Ibrutinib Dose Modifications for Cardiac Failure or Cardiac Arrhythmias

Events	Occurrence	Action
Grade 2 cardiac failure	First	Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (2 capsules [ie, 280 mg daily])
	Second	Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (1 capsules [ie, 140 mg daily])
	Third	Discontinue study drug
Grade 3 cardiac arrhythmias	First	Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (2 capsules [ie, 280 mg daily])[a]
	Second	Discontinue study drug
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue study drug

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

Dose changes must be recorded in the Dosage Administration CRF.

For required dose modification for hepatic impairment refer to Section 5.2.5 and for concomitant treatment with CYP3A inhibitors refer to Section 5.5.2.1.

5.2.4. Treatment-related Lymphocytosis

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood (Stevenson 2011).

Upon initiation of treatment, a transient phase of increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5,000/μL), often associated with reduction of

lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. This effect has also been observed in some patients (33%) with relapsed/refractory mantle cell lymphoma (MCL) treated with ibrutinib. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings as per the IWCLL guidelines (Cheson 2012). In both MCL and CLL, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy and resolves within a median of 8 weeks in the MCL and 14 weeks in the CLL/SLL patients.

A substantial increase in the number of circulating lymphocytes (eg, >400,000/μL) 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 white blood 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.

5.2.5. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver.

- For subjects who develop mild hepatic impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules).
- For subjects who develop moderate hepatic 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).

5.2.6. Warnings, Precautions, and Adverse Effects

5.2.6.1. Warnings and Precautions

Ibrutinib is contraindicated in subjects with clinically significant hypersensitivity to the compound itself or to the excipients in its formulation. Ibrutinib has not been used in subjects with biliary obstruction, acute hepatitis, severe liver failure, or severely impaired renal function; the use of ibrutinib should be avoided in subjects with these conditions. Patients requiring treatment with warfarin will be excluded from studies of ibrutinib. The use of strong CYP3A inhibitors or inducers, grapefruit, and Seville oranges should be avoided for the duration of the study (Appendix G).

5.3. Non-ibrutinib Therapies

The dose and dosing regimen, administration instructions, and procedures for holding a dose, dose reduction, and discontinuation of treatment are to be per package insert and clinical judgment of the investigator.

Relevant warnings, precautions, and a description of possible adverse effects are in the drug product's package insert.

5.4. Treatment Compliance

Patient compliance with the ibrutinib dosing regimen will be assessed by the site pharmacist or designee at each visit using direct questioning, examination of patient diaries, and capsule counts.

Compliance with the ibrutinib dosing regimen will be verified by the Sponsor or designee and will be recorded in the study pharmacy binder. The responsibilities of the pharmacist or designee are as follows:

- 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 the Sponsor's instructions

5.5. Concomitant Medications During Ibrutinib Therapy

5.5.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Patients at Risk for Tumor Lysis Syndrome

Patients with more than 1 of the following factors are considered to be at increased risk of tumor lysis syndrome:

- serum creatinine $\geq$ 1.5 x ULN
- WBC count $\geq$ 50 x 10^9/L (or 50,000/mm^3)
- uric acid > ULN

Such patients should be considered for hydration and treatment with a uric acid lowering agent (xanthine oxidase inhibitor allopurinol or Uloric [febuxostat] +/- rasburicase) according to the drug product's package insert before continuing treatment with study drug, as well as for frequent monitoring for tumor lysis-associated signs and symptoms.

5.5.2. Concomitant Medications to be Used with Caution

5.5.2.1. 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.

- If a strong CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. For subjects who are already on 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 therapy, as these contain moderate inhibitors of CYP3A (see Section 5.2.1).
- No dose adjustment is required in combination with mild inhibitors.

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

A list of common CYP3A inhibitors and inducers is provided in Appendix G. For further information, please refer to the current version of the IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

5.5.2.2. 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. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after ibrutinib.

5.5.3. Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function and supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in patients treated with ibrutinib and the mechanism for the bleeding events is not well

understood. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 5.6).

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

5.5.4. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, or experimental therapy is prohibited while the patient is receiving ibrutinib. Localized, hormonal, or bone sparing treatment for non-B-cell malignancies may be considered with approval of the Medical Monitor.

5.6. 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 to the use of ibrutinib in the perioperative period for patients who require surgical intervention or an invasive procedure while receiving ibrutinib:

5.6.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, skin or needle biopsy, lumbar puncture [other than shunt reservoir access], 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 patient is on ibrutinib, it is not necessary to hold ibrutinib.

5.6.2. Major Surgical Procedures

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

6. STUDY PROCEDURES AND ASSESSMENTS

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.

Every effort should be made to have study assessment and procedures performed at the study center at which the patient was randomized and is receiving treatment.

Study assessments are briefly described below and are described in detail in the schedules of assessments in the appendices: Appendix A, assessments before PD in patients randomized to chlorambucil; Appendix B, assessments before PD in patients randomized to ibrutinib; Appendix C, assessments after PD in patients on second-line ibrutinib‡; and Appendix D, assessments after PD in patients on anticancer treatment other than ibrutinib (ie, non-ibrutinib), or no treatment.

6.1. Informed Consent and Assessment of Eligibility

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

The patient initially consents to participation in this extension study at enrollment in the parent study. Informed consent for participation in the extension study will again be obtained before any extension-study-specific procedures or assessments are performed.

At entry into the extension study, all patients undergo an eligibility visit. The assessments at the visit vary depending on the treatment to which the patient was randomized in the parent study, the disease-progression status at transfer to the extension study, and the planned treatment in the extension study. Assessments at the eligibility visit are described in Appendix A, Appendix B, Appendix C, and Appendix D.

6.2. Randomization and Blinding

This is an open-label study, and treatment assignment in the extension study is not randomized.

6.3. Assessments and Procedures by Visit

Study-visit assessments vary depending on the treatment to which the patient was randomized in the parent study, the disease-progression status at transfer to the extension study, and the planned treatment in the extension study. Assessments in the various patient-subsets are individually listed below.

6.3.1. PCYC-1116-CA Assessments Before PD in Arm A Patients (ie, in patients on chlorambucil in parent study)

Patients randomized to chlorambucil in the parent study (ie, Arm A of the parent study) who have not experienced PD at the time of parent-study closure are transferred to the extension study and are assessed as described below.

The schedule of assessments for these patients is in Appendix A.

6.3.1.1. Eligibility Visit

- Informed consent
- Confirmation of eligibility for PCYC-1116-CA

6.3.1.2. Day 1 of Every 4th Month

Until 25 months after the start of treatment in the parent study, the following assessments occur every 4 months, on Day 1 of the month (ie, Months 13, 17, 21, 25, counting from Cycle 1 Day 1 in the parent study); starting from month 30 onwards, the assessments then occur every 6 months until the patient experiences PD or the study is closed by the Sponsor. Response assessments are to be maintained on the original parent study schedule.

- Concomitant medications (ongoing at the end of the concomitant medications reporting period)
- Identification of alternative anticancer treatment including start date and reason (for patients discontinuing IP for reasons other than PD)
- Adverse events (ongoing at the end of the AE reporting period)
- Other malignancy
- Physical examination
- Vital signs
- ECOG functional status
- Hematology
- Serum chemistry
- Patient reported outcomes (PRO) assessments (EQ-5D-5L, FACiT Fatigue)
- Disease assessment by disease-related symptoms and overall response assessment

The assessments below will occur every 12 months until the patient experiences PD or the study is closed by the Sponsor.

- Disease assessment by computed tomography (CT)/magnetic resonance imaging (MRI) scan
- Bone marrow biopsy and/or aspirate and MRD to be performed if indicated
- Predictive Biomarkers

6.3.1.3. Suspected-PD Visit

This visit occurs as soon as possible after PD is suspected:

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue)
- Concomitant medications (ongoing at the end of the concomitant medications reporting period)
- Adverse events (ongoing at the end of the AE reporting period)
- Other malignancy

- Physical examination
- Vital signs
- ECOG functional status
- Hematology
- Cytogenetic, CLL fluorescence in situ hybridization (FISH) panel
- Disease assessment by CT/MRI scan, disease-related symptoms, and overall response assessment
- Bone marrow biopsy and/or aspirate to be performed if indicated
- Predictive biomarkers

If PD is confirmed and an indication for treatment is present per the IWCLL guidelines, second-line treatment plan is determined, and subsequent assessments are as described in Section 6.3.3 (if eligible for second-line ibrutinib‡) or Section 6.3.4 (for non-ibrutinib therapy or no treatment).

If PD is not confirmed, subsequent assessments are as described in Section 6.3.1.2.

6.3.2. PCYC-1116-CA Assessments Before PD or end of ibrutinib therapy for other reasons in Arm B Patients (ie, in patients randomized to Ibrutinib in parent study)

Patients randomized to ibrutinib in the parent study (ie, Arm B of the parent study) who have not experienced PD at the time of parent-study closure are transferred to the extension study for continued ibrutinib therapy and are assessed as described below.

The schedule of assessments for these patients is in Appendix B.

6.3.2.1. Eligibility Visit

- Informed consent
- Confirmation of eligibility for PCYC-1116-CA

6.3.2.2. Day 1 of Every Study Visit

Until 27 cycles after the start of treatment in the parent study, the following assessments occur on Day 1 of every odd-numbered cycle (ie, Cycles 13, 15, 17, 19, 21, 23, 25, 27 counting from Cycle 1 Day 1 in the parent study); from Cycle 30 onwards, the assessments then occur every 4 cycles until the patient experiences PD or the study is closed by the Sponsor:

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue)
- Concomitant medications
- Adverse events
- Other malignancies
- Physical examination (including focused ocular questions)
- Vital signs

- ECOG functional status
- Hematology
- Serum chemistry
- Disease-related symptoms
- Overall response assessment

Dispense study drug upon completion of assessments.

6.3.2.3. Day 1 of Designated Cycles – Efficacy Assessments

Until 25 cycles after the start of treatment in the parent study, the following assessments occur on Day 1 of every 4th cycle (ie, Cycles 13, 17, 21, 25 counting from Cycle 1 Day 1 in the parent study); starting from Cycle 30 onwards, the assessments then occur every 12 cycles until the patient experiences PD or the study is closed by the Sponsor:

- Disease assessment by CT/MRI scan, disease-related symptoms, and overall response assessment
- Predictive biomarkers
- Bone marrow biopsy and/or aspirate and MRD to be performed if indicated

6.3.2.4. Suspected-PD Visit

This visit occurs as soon as possible after PD is suspected:

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue)
- Physical examination (including focused ocular questions)
- Vital signs
- Adverse events (ongoing at the end of the AE reporting period)
- Concomitant medications (ongoing at the end of the concomitant medications reporting period)
- ECOG functional status
- Hematology
- Cytogenetic, CLL fluorescence in situ hybridization (FISH) panel
- Disease assessment by CT/MRI scan, disease-related symptoms, and overall response assessment
- Predictive Biomarkers
- Bone marrow biopsy and/or aspirate to be performed if indicated

If PD is confirmed and the IWCLL criteria are met for active disease requiring treatment, then the second-line treatment plan is determined, and subsequent assessments are as described in Section 6.3.4.

If PD is not confirmed, subsequent assessments are determined by whether the patient is still receiving ibrutinib:

- If the patient is still receiving ibrutinib at the time of the Suspected-PD Visit, subsequent assessments are as described in Sections 6.3.2.2 and 6.3.2.3.
- If the patient is no longer receiving ibrutinib at the time of the Suspected-PD Visit (eg, ibrutinib was stopped by the investigator when PD was suspected), subsequent assessments are as described in Section 6.3.2.6.

6.3.2.5. End-of-Treatment Visit

The end-of-treatment visit occurs within 30 days after the end of randomized ibrutinib therapy. The assessments are as follows:

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue)
- Concomitant medications
- Adverse events
- Other malignancies
- Physical examination (including focused ocular questions)
- Vital signs
- ECOG functional status
- Hematology
- Serum chemistry
- Disease-related symptoms

6.3.2.6. Pre-PD Follow-up Visits

Until 25 months after the start of treatment in the parent study, pre-PD Follow-up Visits occur every 4 months after the End-of-Treatment Visit for patients who (1) had not experienced PD and (2) had ibrutinib therapy discontinued before the Suspected-PD Visit. Starting from month 30 onwards, these assessments then occur every 6 months until PD or study closure (ibrutinib therapy is not to be restarted in these patients). The assessments are as follows:

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue)
- Physical examination
- Vital signs
- Concomitant medications (ongoing at the end of the concomitant medications reporting period)
- Adverse events (ongoing at the end of the AE reporting period)
- Other malignancies
- ECOG functional status
- Hematology

- Serum chemistry
- Identification of alternative anticancer treatment including start date, reason, duration, and response (for patients discontinuing IP for reasons other than PD)
- Disease assessment by disease-related symptoms and overall response assessment

The assessments below occur every 12 months until PD or study closure:

- Disease assessment by CT/MRI scan
- Predictive Biomarkers
- Bone marrow biopsy and/or aspirate and MRD to be performed if indicated

6.3.3. PCYC-1116-CA Assessments After Disease Progression – Second-line Ibrutinib Therapy‡

Patients who experience PD and then receive second-line therapy ibrutinib therapy are assessed as described below.

The schedule of assessments for these patients is in Appendix C.

6.3.3.1. Eligibility Visit

- Informed consent
- Confirmation of eligibility for PCYC-1116-CA
- Confirmation of eligibility for second-line ibrutinib
- Physical examination (including focused ocular questions)
- Vital signs
- ECOG functional status
- Hematology
- Serum chemistry
- Medical history
- Collect and record the patient's complete history including concurrent medical signs and symptoms that occurred in the intervening period between stopping first-line treatment in the parent study and start of second-line therapy.
- Disease assessment by CT/MRI scan, disease-related symptoms, and overall response assessment (assessments performed in the 8 weeks before the start of second-line therapy can be used)
- Bone marrow biopsy and/or aspirate to be performed if indicated

The physical examination, vital signs assessment, determination of ECOG status, and central-laboratory hematology and serum chemistry tests are not required at the eligibility visit if these assessments have been done in the 7 days before the visit.

6.3.3.2. Day 1 of 1st Cycle on Ibrutinib (must be completed within 14 days of establishing eligibility)

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue)
- Concomitant medications
- Adverse events
- Other malignancies
- Physical examination (including focused ocular questions)
- Vital signs
- ECOG functional status
- Hematology
- Serum chemistry
- Cytogenetic, CLL fluorescence in situ hybridization (FISH) panel
- Predictive biomarkers
- Dispense study drug
- Study drug administration: The first dose of ibrutinib will be taken at the investigational site on Day 1 of Cycle 1 after all procedures are conducted

6.3.3.3. Day 1 of 2nd Through 6th Cycle on Ibrutinib

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue) on Cycles 3 and 5.
- Concomitant medications
- Adverse events
- Other malignancies
- Physical examination (including focused ocular questions)
- Vital signs
- ECOG functional status
- Hematology
- Serum chemistry
- Dispense study drug

The following will be performed on Cycle 5:

- Disease assessment by CT/MRI scan, disease-related symptoms, and overall response assessment
- Predictive biomarkers
- Bone marrow biopsy and/or aspirate and MRD to be performed if indicated

6.3.3.4. Day 1 of Cycles from 7th Cycle on Ibrutinib to Study Closure

Every odd-numbered cycle of ibrutinib therapy starting at the 7th cycle (7th, 9th, 11th, etc., cycle of ibrutinib) until 27 cycles after the start of treatment, then every 3 cycles until PD or study closure starting from Cycle 30, the following assessments are performed for as long as the subject is taking ibrutinib:

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue)
- Concomitant medications
- Adverse events
- Other malignancies
- Physical examination (including focused ocular questions)
- Vital signs
- ECOG functional status
- Hematology
- Serum chemistry
- Dispense study drug

Also, every 4th cycle of ibrutinib until 25 cycles after the start of treatment (ie, Cycles 13, 17, 21, 25), then starting from Cycle 30 onwards, every 6 cycles until PD or study closure, the following additional assessments are performed:

- Disease assessment by CT/MRI scan, disease-related symptoms, and overall response assessment
- Predictive biomarkers
- Bone marrow biopsy and/or aspirate to be performed as indicated

6.3.3.5. Suspected-PD Visit

This visit occurs as soon as possible after PD is suspected; disease status is assessed as follows:

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue)
- Physical examination (including focused ocular questions)
- Concomitant medications (ongoing at the end of the concomitant medications reporting period)
- Adverse events (ongoing at the end of the AE reporting period)
- Vital signs
- ECOG functional status
- Hematology
- Cytogenetic, CLL fluorescence in situ hybridization (FISH) panel
- Disease assessment by CT/MRI scan, disease-related symptoms, and overall response assessment

- Predictive Biomarkers
- Bone marrow biopsy and/or aspirate to be performed as indicated

If PD is confirmed and IWCLL criteria are met for active disease requiring treatment, then a next-line treatment plan is determined, and subsequent assessments are as described in Section 6.3.4.

If PD is not confirmed, subsequent assessments are determined by whether patient is still receiving ibrutinib:

- If the patient is still receiving ibrutinib at the time of the Suspected-PD Visit, subsequent assessments are as described in Sections 6.3.3.2, 6.3.3.3, or 6.3.3.4 (depending on the duration of prior ibrutinib therapy).
- If the subject is no longer receiving ibrutinib at the time of the Suspected-PD Visit (eg, ibrutinib was stopped by the investigator when PD was suspected), subsequent assessments are as described in Section 6.3.3.7.

6.3.3.6. End-of-Treatment Visit

This visit occurs within 30 days of the end of second-line ibrutinib therapy. The visit should be performed before initiation of subsequent anticancer therapy. The assessments are as follows:

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT-Fatigue)
- Concomitant medications
- Adverse events
- Other malignancies
- Physical examination (including focused ocular questions)
- Vital signs
- ECOG functional status
- Hematology
- Serum chemistry
- Disease-related symptoms
- Predictive biomarkers

6.3.3.7. Pre-PD Follow-up Visits

Until 25 months after the start of treatment, these visits occur every 4 months after the End-of-Treatment Visit for patients who (1) had not experienced PD and (2) had ibrutinib therapy discontinued before the Suspected-PD Visit. From 30 months onwards, these assessments then occur every 6 months until PD or study closure (ibrutinib therapy is not to be restarted in these patients). The assessments are as follows:

- Patient-reported outcomes assessments (EQ-5D-5L, FACiT- Fatigue)
- Physical examination
- Concomitant medications (ongoing at the end of the concomitant medications reporting period)
- Adverse events (ongoing at the end of the AE reporting period)
- Other malignancies
- Vital signs
- ECOG functional status
- Hematology
- Serum chemistry
- Identification of alternative anticancer treatment including duration and response (for patients discontinuing IP for reasons other than PD)
- Disease assessment by CT/MRI scan, bone marrow biopsy and/or aspirate and MRD as appropriate, disease-related symptoms, and overall response assessment
- Predictive Biomarkers

6.3.4. PCYC-1116-CA Assessments After Disease Progression – Non-ibrutinib Subsequent Therapy or No Subsequent Therapy

Following implementation of Amendment 3, patients who were randomized to and who subsequently progressed on chlorambucil will not be followed and will exit the study.

Patients who experience PD on first-line ibrutinib and go on to receive an alternative anticancer treatment other than ibrutinib as subsequent therapy or no subsequent therapy will be followed per Appendix D. Until implementation of the present amendment, patients who received non-ibrutinib therapy were potentially eligible to receive subsequent treatment with ibrutinib if they met eligibility criteria outlined in Section 4.2‡. Once the Medical Monitor approved next line ibrutinib therapy, the patient were assessed following the scheduled outlined in Section 6.3.3 (and Appendix C) starting with the eligibility visit‡.

The schedule of assessments for these patients is in Appendix D.

6.3.4.1. Eligibility Visit

- Informed consent
- Confirmation of eligibility for PCYC-1116-CA

6.3.4.2. Follow-up Visits

Patients starting non-ibrutinib subsequent therapy will be followed every 4 months from the start of subsequent therapy with an alternative anticancer treatment. Patients deciding to forego subsequent therapy will be followed every 4 months from the date of decision to forego subsequent therapy.

Following assessments are performed at the frequency described above:

- Survival status
- Identification of alternative anticancer treatment including start date, reason for initiating therapy, duration, and response
- Other malignancies

Predictive Biomarkers will be collected every 12 months.

6.4. Description of Assessments and Procedures

6.4.1. Confirmation of Eligibility

Perform all necessary procedures and evaluations to document that the patient meets each eligibility criterion (Section 4.1). In addition, for patients who are being considered for second-line ibrutinib therapy, perform all necessary procedures and evaluations to document that the patient meets the additional criteria for second-line ibrutinib (Section 4.2)‡. Please refer to the study manual for a more detailed description of the procedures. Blood samples for hematology and serum chemistry tests will be evaluated by a central laboratory to confirm eligibility for second-line ibrutinib‡.

6.4.2. Medical History

Collect and record the patient's complete history including concurrent medical signs and symptoms that occurred in the intervening period between stopping first-line treatment in the parent study and start of second-line ibrutinib therapy‡.

6.4.3. Adverse Events

The accepted regulatory definition of an AE is in Section 8.2. In this long-term extension study, AEs are recorded as follows:

- AE data collected for patients on first-line or second-line ibrutinib within AE reporting period defined in Section 8.3.1. These events are recorded at the study visits identified in the schedules of assessment (Appendix B and Appendix C), when volunteered by the patient, and whenever the investigator becomes aware of an event.
- If AE is reported as ongoing at the time of closure of the parent study, AE data will continue to be collected for patients randomized to chlorambucil. These events are recorded at the study visits identified in the Schedule of Assessment (Appendix A).
- AE data are not collected for patients on second-line therapy with an alternative anticancer treatment other than ibrutinib.

Events must be recorded from the time the ICF is signed (first-line ibrutinib) or from start of eligibility assessments (second-line ibrutinib) until 30 days after the last dose of study drug. A laboratory abnormality that is designated clinically significant by the investigator will be recorded as an AE. AEs of special interest (see Section 8.3.4 for details) will be reported to the

Sponsor within 24 hours of awareness and will require enhanced data collection. Additional important requirements for AE and SAE reporting are explained in Section 8.3.

6.4.4. Physical Examination

Physical examinations should include weight, and examination of the skin, eyes (with specific questions focused on ocular symptoms for ibrutinib patients only), ears, nose, throat, lungs, heart, abdomen, extremities, and lymphatic system. The lymphatic system examination will include bi-dimensional measurements of palpable lymph nodes and measurement of spleen and liver sizes by centimeters below the costal margin on the respective side.

The examination should also include inquiry of ocular symptoms and patients should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.

6.4.5. Vital Signs

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

6.4.6. ECOG Performance Status

The ECOG performance index is provided in Appendix H.

6.4.7. Concomitant Medications

Document all medications from the time of transfer to the extension study through 30 days after the last dose. After a patient discontinues study treatment, receipt of all subsequent anticancer therapies will be collected until patient death or closure of the study.

6.4.8. Patient-reported Outcomes

Two PRO instruments—the EQ-5D-5L (Appendix J) and the FACiT-fatigue (Appendix K)—will be administered in this study. These questionnaires are to be completed by the patient prior to any other study procedures at the designated visits.

6.4.8.1. EQ-5D-5L

The EQ-5D-5L is a standardized instrument used to measure of health outcome (EuroQol Group 1990) and consists of 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 dimensions are used to compute a single utility score ranging from 0 to 1, representing the general health status of the individual. The 5 dimensions evaluated are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

6.4.8.2. FACiT-Fatigue

The FACiT-F questionnaire is a measure of fatigue-related quality of life in patients with cancer and other chronic diseases (Yellen 1997). 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, as well as in patients with cancer (Cella 2002) or rheumatoid arthritis.

6.4.9. 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 laboratory blood samples should be redrawn as soon as possible. In the event that the missing central laboratory sample is unrecoverable, local laboratory results will be collected, if available, and entered in the clinical database for response or progression confirmation.

6.4.10. 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 laboratory blood samples should be redrawn as soon as possible.

6.4.11. Disease Assessment

6.4.11.1. Computed Tomography (CT) Scans

CT scans will be performed as described in the schedules of assessment. MRI may be used to evaluate sites of disease 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 first be discussed with the study's Medical Monitor.

6.4.11.2. Bone Marrow Biopsy and/or Aspirate

A bone marrow aspirate and/or biopsy should be obtained to confirm CR, CRi or to confirm cytopenic progression and distinguish autoimmune and treatment-related cytopenias (Section 7.5.2). Marrow collected to confirm CR should have MRD assessed by flow cytometry on the aspirate. An additional tube of bone marrow aspirate will be collected for biomarker assessments and 2 slides of the aspirate smear submitted.

6.4.11.3. Disease-related Symptoms

Disease-related symptoms—ie, fatigue, night sweats, fever, weight loss, symptoms of splenomegaly (abdominal pain/discomfort including early satiety), and anorexia—will be assessed and recorded.

6.4.11.4. Overall Response Assessment

Overall response assessment will include evaluation of physical examinations, recording of symptoms, hematological evaluations, and radiographic evaluations per the schedule of assessments (see Section 7 and Appendix A, Appendix B, and Appendix C). For any suspected case of disease progression, refer to Section 7.1.

6.4.12. Cytogenetic, CLL FISH Panel

As described in the schedules of assessments, patients at suspected PD and in the 8 weeks before Cycle 1 Day 1 of second-line ibrutinib therapy[1] will have a bone marrow biopsy and/or aspiration performed locally to assess the cytogenetic profile by using the standard CLL FISH probes to detect abnormalities in chromosomes 13q, 12, 11q, and 17p. If bone marrow for FISH is not available, a peripheral blood sample in a patient with a pretreatment lymphocytosis (>10,000 cells/μL) can be subjected to FISH analysis.

6.4.13. Exploratory Investigations of Prognostic and Predictive Biomarkers and Mechanism of Treatment Resistance

Blood samples will be collected as described in the schedules of assessments. These samples will be processed and maintained for downstream testing to evaluate potential biomarkers related to disease response and to investigate potential mechanisms of treatment resistance. These samples may later be 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. These efforts may identify genes and pathways associated with primary or later development of resistance to ibrutinib and potentially identify biomarkers that could assist with future development of this compound.

6.4.14. Alternative Anticancer Treatment

For all patients in pre-PD follow up (Appendix A, Appendix B and Appendix C) and Appendix D, identification of alternative anticancer treatment, including start date, reason, duration, and best overall response (BOR) will be recorded and assessed at each visit according to the visit schedule of assessments.

Following implementation of Protocol Amendment 3, for patients randomized to chlorambucil, identification of alternative anticancer treatment will only include start date and reason.

7. MAIN EFFICACY EVALUATIONS

Disease evaluations include the following:

- Physical examination (which will focus on the presence/absence of size increase/decrease in lymph nodes, liver, and spleen)
- Disease-related symptoms
- Hematologic parameters by CBC performed at a central laboratory
- Radiographic evaluation (CT or MRI scan of the neck, chest, abdomen, and pelvis)
- Bone marrow aspirate and/or biopsy as appropriate by flow cytometry if there is evidence of CR in the other response parameters.
    - Patients who achieve MRD-negative remission in the bone marrow may then be followed by peripheral blood MRD approximately every 6 months.

- Patients who have MRD-positive status in the bone marrow, can also be followed with peripheral blood MRD assessments, however, once the patient becomes MRD-negative in the peripheral blood, this result should be subsequently confirmed with a bone marrow MRD assessment.

Efficacy assessments, for the purpose of the study result analyses, will be performed by the investigator. At the request of Health Authorities, the data may be reviewed by an Independent Review Committee (IRC) as well.

7.1. Suspected Disease Progression

The schedules of assessments are provided in Appendix A, Appendix B, and Appendix C. Any suspected case of disease progression will prompt procedures performed in a Suspected-PD Visit (Section 6.3). Disease progression should be confirmed with a CT scan (or MRI, if CT is contraindicated) and should be reported to the Sponsor within 24 hours of discovery. If disease progression is suspected based on the results of a single examination (including CT scan) or a single laboratory parameter, this finding should be confirmed by a subsequent evaluation at least 2 weeks later.

Study treatment and all study-related procedures and assessments—as described in Appendix A, Appendix B, Appendix C or Appendix D— should be continued until disease progression is determined by the investigator. When disease progression has been determined by the investigator, the current study treatment should be discontinued.

If new anticancer therapy is initiated prior to progressive disease, the patient should continue to be followed for disease progression as described for the pre-PD follow-up phase according to the schedule in which they are enrolled (Section 6.3).

Blood tests performed locally for determination of response or disease progression will need to be repeated by the central laboratory for confirmation of results.

7.2. Guidelines for Disease Evaluation

Objective response will be categorized as CR, CR with incomplete bone marrow recovery (CRi), nPR, PR, stable disease, or PD—all based upon IWCLL criteria (Hallek 2008). All responses must be maintained for at least 2 months to be considered confirmed. CRs must be confirmed by bone marrow biopsy and/or aspirate. Response assessments will occur independent of ongoing therapy.

Detailed definitions of all categories of response are in Appendix E. Response criteria and criteria for disease progression are described in Appendix F.

Given the known mechanism of action of BCR-inhibiting agents, including ibrutinib, and the treatment-related lymphocytosis frequently observed during treatment with ibrutinib, isolated treatment-related lymphocytosis (in absence of other clinical, CT, or laboratory evidence of

disease progression) will not be considered progressive disease. This approach is supported by both the authors of the IWCLL 2008 guidelines (Hallek 2012, Cheson 2012) and the NCCN.

Table 5 outlines what is required for each parameter at baseline to be evaluable throughout the study.

Table 5: Evaluable Parameter Requirements

Parameter	Requirements to be Evaluable for Response
Measurable disease	Lymph node > 1.5 cm
Splenomegaly	Enlarged spleen
Hepatomegaly	Enlarged liver
Lymphocyte count	> 4,000/μL
Platelets	< 100,000/μL
Absolute neutrophil count	< 1,500/μL
Hemoglobin	< 11.0 g/dL

7.3. Sustained Hematological Improvement

In all patients and the subset of patients with cytopenia(s) at baseline (Hgb ≤11 g/dL, platelets ≤100,000/μL), time to improvement in blood counts and percentage of patients with improvement (sustained improvement, defined as improvement in cytopenia by an increase of Hgb levels from baseline by ≥ 2 g/dL, or an increase of platelet counts from baseline by ≥ 50%, with the duration of improvement lasting for at least 56 days without blood transfusion or growth factors) will be assessed.

7.4. Resolution of Pretreatment Disease-Related Symptoms

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

7.5. Treatment-Related Definitions

Definitions of measurable disease, treatment-related lymphocytosis, Richter's transformation, MRD, and treatment failure can be found in Appendix E.

7.5.1. Computed Tomography Scans

Radiological imaging by CT with contrast is required if attainable, and it must include the pelvis, abdomen, chest, and neck. Patients who are intolerant to IV 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.

CT scans of the neck, chest, abdomen, and pelvis will be performed at times specified in the schedules of assessments. In the event disease progression is suspected based on physical examination or a laboratory test, a CT scan must be performed to confirm disease progression.

Up to 6 measurable lymph nodes (target lesions), clearly measurable in 2 perpendicular dimensions, will be followed 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. If additional lesions are present but are not included in the target lesion assessment, they can be added as nontarget lesions followed throughout the study.

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

Lymph nodes and spleen will be evaluated radiographically, and radiographic findings will override physical examination assessment of the same lesion.

Scans will be read by an independent local radiologist, and results will be interpreted by the investigator.

7.5.2. Bone Marrow Aspirate and/or Biopsy and Minimal Residual Disease

If the patient's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved, a bone marrow aspirate and/or biopsy should be obtained to confirm the CR or nPR. In rare cases where progression is only shown in 1 parameter, a bone marrow aspirate and/or biopsy can be performed to confirm cytopenic progression and distinguish autoimmune and treatment-related cytopenias.

Peripheral blood and bone marrow aspirate or biopsy with flow cytometry assessment(s) for MRD should be done if there is evidence of CR in all of the response parameters. MRD is defined as < 1 CLL cell per 10,000 leukocytes. Following the attainment of an MRD-negative CR confirmed by bone marrow aspirate, patients should be followed with peripheral blood MRD analyses approximately every 6 months. Patients who have MRD-positive status in the bone marrow, can also be followed with peripheral blood MRD assessments every 4 to 6 cycles, however, once the patient becomes MRD-negative in the peripheral blood, this result should be subsequently confirmed with a bone marrow MRD assessment.

8. ASSESSMENT OF SAFETY

In this long-term extension study, AEs are recorded as follows:

- AE data collected for patients on first-line or second-line ibrutinib within AE reporting period defined in Section 8.3.1. All AEs are recorded at the study visits identified in the

schedules of assessment for ibrutinib (Appendix B and Appendix C), when volunteered by the patient, and whenever the investigator becomes aware of an event.

- If AE reported as ongoing at the time of closure of the parent study, AE data will continue to be collected for patients randomized to chlorambucil. All AEs are recorded at the study visits identified in the schedule of assessment (Appendix A).
- AE data are not collected for patients on second-line therapy with an alternative anticancer treatment other than ibrutinib.

8.1. Safety Monitoring Plan

A Pharmacovigilance Committee will compare AEs in the study with safety data from the entire clinical trial database for ibrutinib. 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).

8.2. Definitions

8.2.1. 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 AE; rather it may be the cause of an AE. AEs that occur due to disease progression must be reported as all other treatment-emergent AEs.

The term “disease progression” should not be reported as an AE term. As an example, "worsening of CLL/SLL" or the clinical diagnosis that is associated with disease progression should be reported.

AEs 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 8.3.1).
- 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 ICF 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.

8.2.2. 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.

8.2.3. Severity

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of nonhematologic AEs. Refer to Appendix I for the grading of hematologic AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

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

8.2.4. 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.

8.2.5. Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the IB/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 IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the IB/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.

8.3. 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 AEs ongoing at the time of closure of the parent study must be followed up to resolution in the extension study. All SAEs also must be reported on the SAE Worksheet (see Section 8.3.3).

8.3.1. Adverse Event Reporting Period

For patients randomized to ibrutinib in the parent study and continuing on ibrutinib therapy in PCYC-1116-CA, AEs will continue to be reported until 30 days following the last dose of ibrutinib.

For patients who were originally randomized to chlorambucil in the parent study and cross over to the second-line ibrutinib therapy in PCYC-1116-CA, AEs will be reported from the time the patients start eligibility procedures to commence second-line ibrutinib therapy until 30 days following the last dose of ibrutinib.

Patients who were originally randomized to chlorambucil in the parent study and have not crossed over to second-line ibrutinib with AEs ongoing at the time of closure of the parent study will continue to have those AEs monitored until resolution.

If an SAE is present at the End-of-Study 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.

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. Resolution information after 30 days should be provided.

Progressive disease should **not** be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported. 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. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines. 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.

8.3.2. Assessment of Adverse Events

Investigators will assess the occurrence of AEs including SAEs as described in the schedules of assessments for ibrutinib (Appendix B and Appendix C), recording events when volunteered by the patient, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means. Events 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.

8.3.3. 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 AE/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.

8.3.4. Events of Special Interest

Specific AEs, or groups of AEs, 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 8.3.3) and will require enhanced data collection. However, an Event of Special Interest will be considered an SAE only if it meets 1 of the criteria for SAEs. All Events of Special Interest will be submitted without a serious criterion selected if no other serious criterion is met.

8.3.4.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

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

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

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 8.3.4 above.

8.3.5. Pregnancy

Due to the inclusionary ages of this study, it is not expected that female study patients will have the ability to become pregnant.

Before study enrollment, male patients must be willing to 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. A 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 ibrutinib. 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's partner from the time of consent to 30 days after the last dose of ibrutinib. 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.

8.3.6. Eye-Related Adverse Events

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

8.3.7. Other Malignancies

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 in all patients.

8.4. 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 a control group of SAEs from previous studies 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.

8.5. Special Reporting Situations

Special reporting situations on a Sponsor study may require expedited reporting and/or safety evaluation which include, but are not limited to:

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

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an AE, it should be recorded on the AEs eCRF. If the AE is considered serious, it should be recorded on the AEs eCRF as serious and should be reported on the Serious Adverse Event Report Form. The Serious Adverse Event Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness.

9. 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.

9.1. Discontinuation of Treatment

Treatment will be discontinued in the event of any of the following circumstances:

- Progressive disease
- Unacceptable toxicity: an intercurrent illness or adverse event that prevents further ibrutinib administration

- Withdrawal of consent for treatment by patient
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or the best interest of the patient)
- Completion of treatment per Protocol Amendment 3
- Study termination by Sponsor
- Patient becomes pregnant

All patients, regardless of reason for discontinuation of study treatment will undergo an End-of-Treatment Visit and be followed for progression and survival.

The Investigator should notify the Sponsor within 24 hours if a patient discontinues ibrutinib therapy due to disease progression and should provide documentation of disease progression for review by the Sponsor's Medical Monitor. If a patient shows signs of disease progression on physical examination or laboratory assessment, the patient may continue study treatment until disease progression is confirmed. These patients should stay in the study to be followed for survival.

9.2. Withdrawal from the Study

Withdrawal from the study (including all follow-up requirements) will occur under the following circumstances:

- Withdrawal of consent for follow-up by the patient
- Lost to follow-up
- Completion of study under Protocol Amendment 3
- Study termination by Sponsor
- Death

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. STATISTICAL CONSIDERATIONS

This section outlines the general statistical analysis approaches intended for the safety and efficacy analyses for the study. Detailed analyses will be described in the final statistical analysis plan (SAP).

Data from Study PCYC-1115-CA and Study PCYC-1116-CA will be combined at the subject level for safety and efficacy analyses.

10.1. Endpoints

- PFS on first-line therapy
- Progression Free Survival after initiation of subsequent anticancer therapy (PFS2)
- Overall survival
- Time to next treatment
- ORR and DOR
- Safety as measured by all AEs and SAEs
- Disease outcome following cessation of ibrutinib therapy after attainment of minimal residual disease (MRD)-negative remission in those patients receiving ibrutinib as second-line therapy

10.2. Randomization

This study is an extension study of PCYC-1115-CA and includes only a qualified subset of the subjects from the PCYC-1115-CA Study. It is an open-label, non-randomized study.

10.3. Sample-Size Considerations

As this is an extension study, no formal power calculations were performed. The sample size will be the number of patients who are transferred to this study after IRC-confirmed disease progression in the parent study or closure of the parent study. Accuracy of estimation for each efficacy endpoint will depend on the number of available patients in a relevant subgroup defined by line of therapy.

10.4. Planned Analysis

This extension study will remain open and study follow-up will continue approximately 10 years from randomization of the first patient in the parent PCYC-1115-CA Study. Efficacy and safety analysis for the study endpoints will be performed periodically as appropriate.

10.5. Analysis Populations

10.5.1. Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all randomized patients in Study PCYC-1115-CA. All efficacy analyses will be performed based on the ITT population unless otherwise specified, and patients will be analyzed as randomized for the analyses related to first-line therapy and OS.

10.5.2. Safety Population

The safety population for first-line therapy includes all patients who received at least 1 dose of study drug in Study PCYC-1115-CA, either chlorambucil or ibrutinib.

10.6. Control for Bias

The PCYC-1115-CA randomization code will be controlled through a centralized procedure and will not be known to personnel directly involved with study conduct or data analysis in both Study PCYC-1115-CA and Study PCYC-1116-CA until the PCYC-1115-CA database portion is locked and unblinded. Subsequent to sponsor unblinding, study will be fully open-label.

10.7. Efficacy Analyses

10.7.1. Progression-free Survival

PFS on first-line therapy is defined as the time from the date of randomization to disease progression determined by the investigator or death from any cause, whichever occurs first. PFS on first-line therapy will be analyzed in the ITT population. Patients who do not progress in the parent study and do not enroll in Study PCYC-1116-CA will be censored at the last disease assessment performed by investigator in Study PCYC-1115-CA.

PFS2 will be analyzed for ITT patients. It is defined as the time interval between the date of randomization and date of event, which is defined as progressive disease as assessed by investigator that occurs after the next line of subsequent anticancer therapy (including cross-over to ibrutinib), death from any cause, or the start of a second subsequent anticancer therapy if no progressive disease is recorded. Those who do not receive subsequent therapy or do not experience the event as specified above are censored at the last disease assessment without second disease progression.

The analysis for PFS on first-line therapy will follow the primary method described in the PCYC-1115-CA protocol and the SAP, except that a stratified log-rank test will be purely descriptive. The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazard model stratified by the randomization stratification factors (Rai stage and ECOG performance score). Median PFS2 and its 95% confidence interval (CI) will be estimated using the Kaplan-Meier method.

10.7.2. Overall Response Rate

ORR is defined as the crude proportion of patients who achieve a CR, CRi, nPR, or PR as determined by the investigator. Patients who achieve a PR with lymphocytosis will not be included in the ORR. Patients with no post-dose disease assessment will be considered -non-responders. The ORR is estimated with an exact 95% confidence interval. Analysis detail will be defined in the statistical analysis plan.

10.7.3. Duration of Response

To adequately reflect the duration of time during which patients are experiencing tumor reduction and significant benefit in terms of disease control, DOR will be computed for the responders subset based on the response criteria (Section 10.7.2), and will include duration when a responder achieves a PR with lymphocytosis. Hence, DOR estimated by the Kaplan-Meier

method is defined as the interval between the date of initial documentation of a response, including PR with lymphocytosis, and the date of first documented evidence of progressive disease, death, or date of censoring if applicable. Non-responders are excluded from the analysis for DOR. Subjects who are progression-free and alive or have unknown survival status will be censored at the last disease assessment. Analysis detail will be defined in the statistical analysis plan.

10.7.4. Disease Outcome Following MRD-Negative CR

At the investigator's discretion, patients receiving second-line ibrutinib therapy who achieve and retain MRD-negative CR for 6 cycles can have their ibrutinib discontinued. If second-line ibrutinib is discontinued, the patient will be followed for MRD recurrence. A 6-month MRD-negative CR rate per the same evaluable subgroup defined for ORR (Section 10.7.3) and the recurrence rate based on a subset of patients who achieve a 6-month MRD-negative CR will be calculated.

MRD-negative subjects who experience confirmed MRD-positive relapse and/or clinical disease progression by IWCLL criteria may restart ibrutinib therapy.

10.7.5. Overall Survival

OS is defined as the time from randomization to death due to any cause. Patients who are known to be alive or whose survival status is unknown will be censored at the last date the patient is known to be alive. Patients who are lost to follow-up without any post baseline assessments/visits will be censored at the date of randomization. Survival rate at landmark points will be summarized by first-line treatment arm using Kaplan-Meier estimates.

10.8. Safety Analyses

Safety analyses will be presented in accordance with the treatment actually received by patients.

Non-hematological AEs reported by the investigator will be graded according the current version of the NCI CTCAE v4.03. Hematologic toxicity will be assessed by the IWCLL 2008 criteria for grading hematologic toxicity in CLL studies. Verbatim descriptions of AEs will be coded to a preferred term and mapped to System Organ Class using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs that started after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of subsequent therapy, which occurs earlier, are considered treatment emergent. All treatment-emergent AEs will be tabulated using standard methods.

All laboratory values will be converted to standard international units (SI units). Hematologic toxicity will be graded according to the IWCLL criteria (Hallek 2008). All other gradable laboratory parameters will be graded using the NCI CTCAE. Standard methods for summarizing laboratory variables will be used, including the use of summary statistics and shift tables.

11. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

11.1. 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.

11.2. 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 ICF 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.

11.3. 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.

11.4. 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).

11.5. 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 11.3), 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.

11.6. 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.

11.7. Case Report Forms and Record Maintenance

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.

11.8. Investigational Study Drug Accountability

Ibrutinib and any Pharmacyclics-supplied comparator 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 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 Pharmacyclics-supplied comparator must be maintained and readily available for regular inspections 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 additional details on investigational study drug management, please refer to the Pharmacy Manual.

11.9. 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.

11.10. Investigator Responsibilities

A complete list of investigator responsibilities is 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.

11.11. 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.

11.12. 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 sub-investigator (as designated on the Form FDA 1572) 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.

11.13. 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.

The ICF will include a description of treatment in the event of a study related injury and handling of the costs associated therewith, 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.

11.14. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the regulatory authorities and/or IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of regulatory authorities, IRB/REB/IEC and required site approval, as applicable, 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.

11.15. 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.

11.16. 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.

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13. APPENDICES

Appendix A. Schedule of Assessments: PCYC-1116-CA Assessments Before PD in Arm A Patients (ie, in patients on chlorambucil in parent study)

Patients randomized to chlorambucil in the parent study (ie, Arm A of Study PCYC-1115-CA) who have not experienced PD at the time of parent-study closure are transferred to this extension study and assessed as follows.

Assessments	Eligibility Visit	Designated Months Day 1	Suspected-PD Visit[b]
Study visit window	±7 d of parent study closure	±7 d	As soon as possible after suspected PD
Informed consent for PCYC-1116-CA	x		
Confirmation of eligibility for PCYC-1116-CA	x		
Patient-reported outcomes (PRO)[d]		x[a]	x
Adverse events		x[e]	x[e]
Concomitant medications		x[e]	x[e]
Other malignancies		x[a]	x
Identification of alternative anticancer therapy		x[f]	x[f]
Physical examination, vital signs, ECOG		x[a]	x
Hematology		x[a]	x
Serum chemistry		x[a]	
Cytogenetic, CLL FISH panel			x
Predictive Biomarkers		x[g]	x
Disease assessment:			
CT/MRI scan		x[g]	x
Bone marrow biopsy and/or aspirate		(x)[g, c]	(x)
Disease-related symptoms		x[a]	x
Overall response assessment		x[a]	x

CT=computed tomography; d=day; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; PD=progressive disease; ( )=as appropriate to confirm CR or evaluate PD.

Note: Extension study continues for approximately 10 years from randomization of first patient in parent study (ie. PCYC-1115-CA).

a. Until 25 months after the start of treatment in the parent study, the following assessments occur every 4 months, on Day 1 of the month (ie, Months 13, 17, 21, 25, counting from Cycle 1 Day 1 of the parent study); starting from month 30 onwards, the assessments then occur every 6 months until the patient experiences PD or study is closed by the Sponsor.

b. If PD is confirmed and the IWCLL treatment guidelines indicate that new anticancer therapy is indicated, patient will exit the study. If PD is not confirmed, subsequent assessments are as described under "Designated Months/Day 1."

[c] Bone marrow biopsy and/or aspirate should be performed to confirm complete response (CR) or nPR, when appropriate, to evaluate cytopenia. Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; patients confirmed as MRD-negative in the marrow should be followed approximately every 6 months for MRD by peripheral flow cytometry (Section 6.4.11.2). Patients who have MRD-positive status in the bone marrow, can also be followed with peripheral blood MRD assessments every 4 to 6 months, however, once the patient becomes MRD-negative in the peripheral blood, this result should be subsequently confirmed with a bone marrow MRD assessment.

[d] To be completed before any other procedures or physician interactions; includes EQ-5D-5Land FACiT-Fatigue instruments

[e] Only adverse events and concomitant medications ongoing at the end of AE/concomitant medications reporting period will be followed-up to resolution.

[f] Patients discontinuing IP for reasons other than PD must be monitored for alternative anti-cancer treatment including start date and reason.

[g] Every 12 months or earlier if PD is suspected.

Appendix B. Schedule of Assessments: PCYC-1116-CA Assessments Before PD in Arm B Patients (ie, in patients on Ibrutinib in parent study)

Patients randomized to ibrutinib in the parent study (ie, Arm B of Study PCYC-1115-CA) who have not experienced PD at the time of parent-study closure are transferred to the extension study and assessed as follows.

Assessments	Eligibility Visit	Designated Cycles Day 1	Suspected-PD Visit[d]	End-of-Treatment Visit[e]	Pre-PD Follow-up Visits[f]
Study visit window	±7 d of parent study closure	±7 d	As soon as possible after suspected PD	Within 30 d after end of ibrutinib therapy	±7 d
Informed consent for PCYC-1116-CA	x				
Confirmation of eligibility for PCYC-1116-CA	x				
Patient-reported outcomes (PRO)[h]		x[a]	x	x	x
Concomitant medications		x[a]	x[k]	x	x[k]
Adverse events[c]		x[a]	x[k]	x	x[k]
Other malignancies		x[a]		x	x
Identification of alternative anticancer therapy					x[j]
Physical examination[i], vital signs, ECOG		x[a]	x	x	x
Hematology		x[a]	x	x	x
Serum chemistry		x[a]		x	x
Cytogenetic, CLL FISH panel			x		
Disease assessment:					
CT/MRI scan		x[b]	x		x[b]
Bone marrow biopsy and/or aspirate		(x)[b,g]	(x)		(x)[b,g]
Disease-related symptoms		x[a]	x	x	x
Overall response assessment		x[a]	x		x
Predictive biomarkers		x[b]	x		x[b]
Ibrutinib Dispensing and Administration for Patients on Continuing Ibrutinib Therapy					
Patients enroll at their final dose administered in parent study	Dispensed every odd-numbered cycle (ie, Cycles 13, 15, 17, 19, 21, 23, 25, 27 counting from Cycle 1 Day 1 in the parent study); from Cycle 30 onwards, dispensed every 4 cycles; continuous daily dosing				

CT=computed tomography; d=day; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; PD=progressive disease; ( )=as appropriate
Note: Extension study continues for approximately 10 years from randomization of first patient in parent study (ie. PCYC-1115-CA).

a. Until 27 cycles after the start of treatment in the parent study, the following assessments occur on Day 1 of every odd-numbered cycle (ie, Cycles 13, 15, 17, 19, 21, 23, 25, 27 counting from Cycle 1 Day 1 in the parent study); from Cycle 30 onwards, the assessments then occur every 4 cycles until the patient experiences PD or the study is closed by the Sponsor.

b. Until 25 cycles after the start of treatment in the parent study, the following assessments occur on Day 1 of every 4th cycle (ie, Cycles 13, 17, 21, 25, counting from Cycle 1 Day 1 in the parent study); from Cycle 30 onwards, the assessments then occur every 12 cycles (every 12 months for pre-PD follow-up) until the patient experiences PD or the study is closed by the Sponsor.

c. Adverse events are recorded at designated study visits, when volunteered by the patient, and whenever the investigator becomes aware of an event. 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.

d. If PD is confirmed and the IWCLL treatment guidelines indicate that new anticancer therapy is indicated, second-line treatment plan is established and subsequent assessments are as described in Appendix D. If PD is not confirmed, subsequent assessments are determined by whether patient is still receiving ibrutinib:
   - If the patient is still receiving ibrutinib at the time of the Suspected-PD Visit, subsequent assessments are described under "Designated Cycles/Day 1"
   - If the patient is no longer receiving ibrutinib at the time of the Suspected-PD Visit, subsequent assessments are described under "Pre-PD Follow-up Visits." ibrutinib is not to be restarted in these patients.

e. Visit that follows the end of randomized ibrutinib therapy

f. This visit provides follow-up for patients in whom PD is not confirmed but who were no longer receiving ibrutinib at the time of the Suspected-PD Visit (eg, ibrutinib was stopped by the investigator when PD was suspected). Until 25 months after the start of treatment in the parent study, pre-PD Follow-up Visits occur every 4 months after the End-of-Treatment Visit for patients who (1) had not experienced PD and (2) had ibrutinib therapy discontinued before the Suspected-PD Visit. Starting from month 30 onwards, these assessments then occur every 6 months until PD or study closure (ibrutinib therapy is not to be restarted in these patients).

g. Bone marrow biopsy and/or aspirate should be performed to confirm complete response (CR) or nPR, when appropriate, to evaluate cytopenia. Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; patients confirmed as MRD-negative in the marrow should be followed approximately every 6 cycles for MRD by peripheral flow cytometry (see Section 6.4.11.2). Patients who have MRD-positive status in the bone marrow, can also be followed with peripheral blood MRD assessments every 4 to 6 cycles, however, once the patient becomes MRD-negative in the peripheral blood, this result should be subsequently confirmed with a bone marrow MRD assessment.

h. To be completed before any other procedures or physician interactions; includes EQ-5D-5L and FACiT-Fatigue instruments.

i. Includes focused ocular questions (not required for pre-PD).

j. Patients discontinuing IP for reasons other than PD must be monitored for alternative anti-cancer treatment including start date, reason, duration, and response.

k. Only adverse events and concomitant medications ongoing at the end of AE/concomitant medications reporting period will be followed-up to resolution.

Appendix C. Schedule of Assessments: PCYC-1116-CA Assessments After PD – Second-line Ibrutinib Therapy[z]

Patients who experienced PD and receive ibrutinib as second-line therapy are assessed as follows.

Assessments	Eligibility Visit	1st Cycle on ibrutinib	2nd-6th Cycles on ibrutinib	7th Cycle on ibrutinib to Study Closure	Suspected-PD Visit[g]	End-of-Treatment Visit	Pre-PD Follow-up Visit[e,h]
		Day 1 (within 14 days of establishing eligibility)	Day 1	Day 1			
Study visit window		+14 d	±7 d	±7 d	As soon as possible after suspected PD	Within 30 d after end of ibrutinib therapy	±7 d
Informed consent for PCYC-1116-CA	x						
Confirmation of eligibility for PCYC-1116-CA	x						
Confirmation of eligibility for 2nd-line ibrutinib	x						
Medical History	x						
Patient-reported outcomes (PRO)[l]		x	x[m]	x[c]	x	x	x
Concomitant medications		x	x	x[c]	x[p]	x	x[p]
Adverse events[f]		x	x	x[c]	x[p]	x	x[p]
Other malignancies		x	x	x[c]		x	x
Identification of alternative anticancer therapy							x[o]
Physical examination[k], vital signs, ECOG	x[i]	x	x	x[c]	x	x	x
Hematology	x[i]	x	x	x[c]	x	x	x
Serum chemistry	x[i]	x	x	x[c]		x	x
Disease assessment:							
CT/MRI scan	x[a]		x[b]	x[d]	x		x
Bone marrow biopsy and/or aspirate	x[a]		(x)[b, j]	(x)[d, j]	(x)		(x)[j]
Disease-related symptoms	x[a]		x[b]	x[d]	x	x	x
Overall response assessment	x[a]		x[b]	x[d]	x		x
Cytogenetic, CLL FISH panel		x			x		
Predictive biomarkers		x	x[b]	x[d]	x	x	x

Ibrutinib Dispensing and Administration for Patients on Second-line Ibrutinib Therapy				
Ibrutinib 420 mg qd, PO		Dispensed every odd-numbered cycle (ie, Cycles 13, 15, 17, 19, 21, 23, 25, 27 counting from Cycle 1 Day 1 in the parent study); from Cycle 30 onwards, dispensed every 3 cycles; continuous daily dosing[n]		

CLL=chronic lymphocytic leukemia; CT=computed tomography; d=day; ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in situ hybridization; MRI=magnetic resonance imaging; PD=progressive disease; PO=oral; qd=once daily; ( )=as appropriate
Note: Duration of extension study is approximately 10 years from randomization of first patient in parent study (ie. PCYC-1115-CA).

a. Assessment performed in the 8 weeks before the start of second-line therapy can be used.

b. Done at Cycle 5 of ibrutinib only

c. Every odd-numbered cycle of ibrutinib therapy starting at the 7th cycle (7th, 9th, 11th, etc., cycle of ibrutinib) until 27 cycles after the start of treatment, then every 3 cycles until PD or study closure starting from Cycle 30.

d. Assessments performed every 4th cycle of ibrutinib until 25 cycles after the start of treatment (ie, Cycles 13, 17, 21, 25), then starting from Cycle 30 onwards, every 6 cycles until PD or study closure.

e. Until 25 months after the start of treatment, these visits occur every 4 months after the End-of-Treatment Visit, for subjects who (1) had not experienced PD and (2) had ibrutinib therapy discontinued before the Suspected-PD Visit. From 30 months onwards, these assessments then occur every 6 months until PD or study closure (ibrutinib therapy is not to be restarted in these subjects).

f. Adverse events are recorded at designated study visits, when volunteered by the patient, and whenever the investigator becomes aware of an event. All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported an event of special interest for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

g. If PD is confirmed and the IWCLL treatment guidelines indicate that new anticancer therapy is indicated, second-line treatment plan is established and subsequent assessments are as described in Appendix D. If PD is not confirmed, subsequent assessments are determined by whether the patient is still receiving ibrutinib:
   - If the patient is still receiving ibrutinib at the time of the Suspected-PD Visit, subsequent assessments are described under "1st Cycle on ibrutinib, "2nd-6th Cycles on ibrutinib," or "7th Cycle on ibrutinib to Study Closure" (depending on the duration of the patient's prior exposure to ibrutinib).
   - If the patient is no longer receiving ibrutinib at the time of the Suspected-PD Visit, subsequent assessments are described under "Pre-PD Follow-up Visits." Ibrutinib is not to be restarted in these patients.

h. This visit provides follow-up for patients in whom PD is not confirmed but who were no longer receiving ibrutinib at the time of the Suspected-PD Visit (eg, ibrutinib was stopped by the investigator when PD was suspected).

i. Not required if done in preceding 7 days (laboratory tests must have been done by central laboratory)

j. Bone marrow biopsy and/or aspirate should be performed to confirm complete response (CR) or nPR, when appropriate, to evaluate cytopenia. Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; patients confirmed as MRD-negative in the marrow should be followed approximately every 6 cycles for MRD by peripheral flow cytometry (see Section 6.4.11.2). Patients who have MRD-positive status in the bone marrow, can also be followed with peripheral blood MRD assessments every 4 to 6 cycles, however, once the patient becomes MRD-negative in the peripheral blood, this result should be subsequently confirmed with a bone marrow MRD assessment.

k. Includes focused ocular questions (not required for pre-PD).

l. To be completed before any other procedures or physician interactions; includes EQ-5D-5L and FACiT-Fatigue instruments

m. Done at Cycle 3 and Cycle 5.

n. The first dose of ibrutinib on Day 1 of Cycle 1 will be taken at the investigational site after all procedures are conducted.

o. Patients discontinuing IP for reasons other than PD must be monitored for alternative anti-cancer treatment including duration and response.

p. Only adverse events and concomitant medications ongoing at the end of AE/concomitant medications reporting period will be followed-up to resolution.

After implementation of Protocol Amendment 3, the patients who experienced PD and received second-line ibrutinib therapy will exit the study. These patients may be candidates for another long-term extension study (ie, other than Study PCYC-1116-CA) made available for active patients who choose to continue on ibrutinib on a clinical protocol when access to commercial ibrutinib is not feasible.

In order to minimize or avoid treatment interruptions, the patients on second-line ibrutinib opting to move to another long-term extension study, may be allowed to continue treatment within this study for a limited time before transitioning to the other study.

Appendix D. Schedule of Assessments: PCYC-1116-CA Assessments After PD – Subsequent Therapy (Non-ibrutinib) or No Subsequent Therapy

Patients randomized to and progressed on chlorambucil will not be followed on Appendix D and will exit the study.

Patients randomized to and progressed on first-line ibrutinib will be followed on Appendix D. Patients who experienced PD and whose subsequent therapy is any drug other than ibrutinib, patients who experienced PD and who do not meet the IWCLL criteria for requiring additional therapy, and patients who experienced PD and elected not to receive anticancer treatment after PD, are assessed as follows.

Patients who receive non- ibrutinib therapy may be eligible to receive subsequent treatment with ibrutinib if they meet eligibility criteria outlined in Section 4.2‡. Once the Medical Monitor approves next line ibrutinib therapy, the patient will be assessed following the scheduled outlined in Section 6.3.3 (and Appendix C) starting with the eligibility visit‡.

Assessments	Eligibility Visit	Follow-up Visits (every 4 months[b])
Study visit window		±7 d
Informed consent for PCYC-1116-CA	x	
Confirmation of eligibility for PCYC-1116-CA	x	
Survival status		x
Identification of alternative anticancer therapy		x[d]
Predictive Biomarkers		x[c]
Other malignancies		x[a]

IWCLL= International Workshop on Chronic Lymphocytic Leukemia; non-ibrutinib=alternative anticancer treatment other than ibrutinib; PD=progressive disease; ( )=as appropriate

Note: Extension study continues for approximately 10 years from randomization of first patient in parent study (ie. PCYC 1115-CA).

[a] 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.

[b] Patients starting non-ibrutinib subsequent therapy will be followed every 4 months from the start of subsequent therapy with an alternative anticancer treatment. Patients deciding to forego subsequent therapy will be followed every 4 months from the date of decision to forego subsequent therapy.

[c] To be collected every 12 months.

[d] Identification of alternative anticancer treatment will include start date, reason for initiating therapy, duration, and response.

Appendix E. Definitions of Response (Hallek 2008)

Complete Response (CR)

All of the following are required for a CR:

- No significant lymphadenopathy (> 1.5 cm) by CT or palpable on examination (if not scannable)
- No hepatosplenomegaly by CT
- No constitutional symptoms, defined as: no fever > 38ºC for ≥ 2 weeks without evidence of infection, no unintentional ≥10% body weight loss within last 6 months, no night sweats for > 1 month without evidence of infection, and no fatigue (ECOG performance score ≥ 2) interfering with work or usual activities
- ANC > 1500/µL, platelets > 100,000/µL, and hemoglobin > 11.0 g/dL
- Lymphocyte count < 4.0 x 10^9/L

Marrow aspirate and/or 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 < 30% of nucleated cells being lymphocytes. B-lymphoid nodules should be absent. In addition, in patients who meet the CR criteria, MRD by flow cytometry should be performed to evaluate MRD status.

Complete Response with an Incomplete Marrow Recovery (CRi)

CRi is defined as a CR with an incomplete recovery of the patient's bone marrow. Bone marrow must be hypocellular. Patients who have a CRi fulfill criteria for a CR, but continue to have persistent anemia, thrombocytopenia, or neutropenia due to drug toxicity in the bone marrow and not due to any evidence of CLL.

Nodular Partial Response (nPR)

Nodular partial response (nPR) is a response where patients meet criteria for a CR, but the bone marrow biopsy shows that there are still B-lymphoid nodules present. These nodules are residual disease and therefore the patient is termed an nPR.

Partial Response (PR)

At least two of the Category A parameters must be met; with one exception: subjects who only have abnormal lymph nodes at baseline. For this exception, subjects will only need to meet the lymph node response criteria.

- ≥ 50% decrease in the sum products of up to 6 lymph nodes, by CT or, if only one measurable lymph node at baseline, a ≥ 50% decrease in the longest diameter of the single lymph node by CT AND no increase in any other lymph node by CT. Note: In a small lymph node < 2 cm, an increase of < 25% is not considered to be significant.
- No new enlarged lymph nodes by CT or physical examination
- ≥ 50% decrease in the enlargement of spleen and/or liver size from baseline or normalization by CT
- If abnormal at baseline, a ≥ 50% drop in lymphocyte count from baseline or ≤ 4.0 x 10^9/L

Plus a response in at least one of the following criteria independent of growth factor support or transfusion* If all criteria are normal at baseline, they must remain normal to be considered a PR:

- ANC > 1500/µL, or ≥ 50% improvement over baseline
- Platelets > 100,000/µL, or ≥ 50% improvement over baseline
- Hemoglobin > 11.0 g/dL, or ≥ 50% improvement over baseline

* Note: For a criterion to be considered a response, it must have been evaluable at baseline.

PR with Lymphocytosis

If abnormal lymphocyte count at baseline and response criteria (≥ 50% drop in lymphocyte count from baseline or ≤ 4.0 x 10^9/L) has not been met and patient responds in only one other Category. A parameter below, then the response is considered PRL.

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

Plus a response in at least one of the following criteria independent of growth factor support or transfusion. * If all criteria are normal at baseline, they must remain normal to be considered a PR:

- ANC > 1500/µL or ≥ 50% improvement over baseline
- Platelets > 100,000/µL or ≥ 50% improvement over baseline
- Hemoglobin > 11.0 g/dL, or ≥ 50% improvement over baseline

* Note: For a criterion to be considered a response, it must have been evaluable at baseline.

Stable Disease

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

Progressive Disease

At least ONE of following:

- New enlarged nodes > 1.5 cm, new hepatomegaly, or new splenomegaly
- ≥ 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 the nadir count if confirmed by central lab on ≥ 2 serial assessments if the ALC is ≥ 30,000/µL and lymphocyte doubling time is rapid, unless considered treatment

related lymphocytosis New cytopenia (hemoglobin or platelets) attributable to CLL. The progression of any cytopenia (unrelated to autoimmune cytopenia or bleeding), as documented by a decrease of hemoglobin levels from baseline by more than 2 g/dL or to < 10.0 g/dL, or by a decrease of platelet counts from baseline by more than 50% or to < 100,000/μL in the presence of active CLL defines disease progression. When applicable, a marrow biopsy should demonstrate an infiltrate of clonal CLL cells.

- Unequivocal progression for non-target lesions
- Transformation to a more aggressive histology (eg, Richter's Syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.

Suspected progressive disease must be confirmed by a serial examination at least 2 weeks later.

Measurable Disease

Patients must have at least 1 measurable site of disease to participate in the parent 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 its longest diameter. Measurement must be determined by imaging evaluation.

Patients may have a previously irradiated area from a malignancy prior to development of CLL. 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 to have occurred, if progression is confirmed by the investigator.

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 appropriate, including peripheral blood counts.

Treatment-related Lymphocytosis

Treatment-related lymphocytosis is defined as an elevation in blood lymphocyte count of ≥ 50% compared with baseline that occurs in the setting of unequivocal improvement in at least 1 other disease-related parameter including lymph node size, spleen size, hematologic parameters (hemoglobin and platelet count), or disease-related symptoms. Treatment-related lymphocytosis is isolated lymphocytosis occurring when no other criteria for progressive disease are met. In this particular study, it will not be considered progressive disease. This is supported by the most recent version of the NCCN NHL 2016 guidelines.

Richter's Transformation

Richter's syndrome is lymphomatous transformation to a more aggressive histology in a patient with CLL or SLL and 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 must be confirmed with a biopsy (ie, lymph node) demonstrating the histologic transformation.

Minimal Residual Disease (MRD)

MRD is defined as < 1 CLL cell per 10,000 leukocytes, as assessed by flow cytometry of a bone marrow aspirate and/or biopsy or peripheral blood sample. Patients who achieve a complete response (CR) should be evaluated for eradiation of disease cells as determined by flow cytometry on the bone marrow aspiration when available. Patients who achieve MRD-negative remission in the bone marrow may then be followed by peripheral blood MRD approximately every 6 cycles depending on their visit schedule. Patients who have MRD-positive status in the bone marrow, can also be followed with peripheral blood MRD assessments, however, once the patient becomes MRD-negative in the peripheral blood, this result should be subsequently confirmed with a marrow MRD assessment.

Appendix F. 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] Subjects with treatment-related lymphocytosis should remain on study treatment in the absence of other criteria for progressive disease (see Section 7.2). For subjects without treatment-related lymphocytosis, PD by lymphocyte count can be considered based on ≥50% increase from the nadir count if confirmed by central lab on ≥2 serial assessments if the ALC is ≥30,000/µL and lymphocyte doubling time is rapid.

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 subjects have to lack disease related constitutional symptoms. Bone marrow and aspirate is required to confirm CR.
PR: At least two of the Group A parameters must be met; with two exceptions: 1) subjects who only have abnormal lymph nodes at baseline, or 2) subjects who have only abnormal lymph node and abnormal lymphocyte count (ALC) at baseline. For these two exceptions, subjects will only need to meet the lymph node response criteria.
In addition to the Group A criteria, all subjects must also have a response in at least one of the Group B criteria.
SD: the absence of PD and the failure to achieve a response.
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, Hallek 2012, Hallek 2013

Appendix G. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A are defined as follows. Refer to Section 5.5.2.1 on instructions for concomitant use of CYP3A inhibitors or inducers with ibrutinib. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

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

[a] Based on PBPK simulations, up to 9.7-fold increase in AUC and 6.2-fold increase in Cmax 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 H. ECOG Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status[a]
0	Fully active, able to carry on all pre-disease 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.

a Oken, MM, Creech, RH, Tormey, DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 1982; 5:649-655.

Source: http://www.ecog.org/general/perf_stat html; accessed 04 January 2008

Appendix I. 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 x 10^9/L, toxicity will be considered Grade 4. If the baseline platelet count is <20 x 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 J. 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

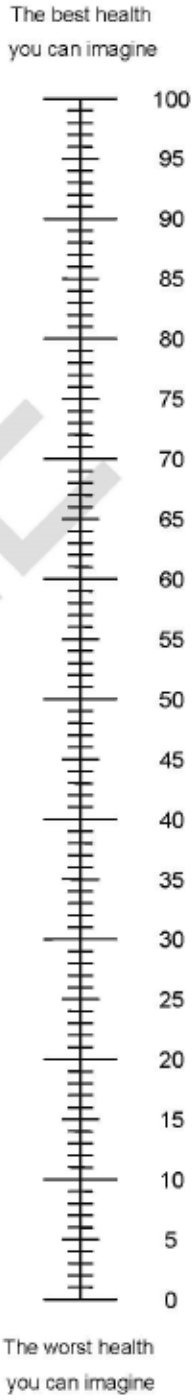
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 K. 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
H7	I feel fatigued	0	1	2	3	4
H12	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 L. Child-Pugh Score for Subjects with Liver Impairment*

(*Child-Pugh Score to be used only in subjects with chronic liver disease)

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.

‡ **Note: second-line ibrutinib is not applicable after implementation of Protocol Amendment 3.**

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Protocol/Protocol Amendment Approval Form

Date circulated for review: 16-Sep-2022

Purpose: Protocol Amendment

Study Number: PCYC-1116-CA

Protocol Version date (DD MMM YYYY): 30 October 2022

☐ **Original**
☒ **Amendment – Version # 4**

Protocol Title: An Open-label Extension Study in Patients 65 Years or Older with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib versus Chlorambucil)

Please indicate that you have reviewed and approve the document listed above by signing and dating below.

Approval Signatures		
Name	**Signature**	**Approval Date**
Clinical Science ☐ NA [redacted]	[redacted]	10/10/22
Clinical Operations ☐ NA [redacted]	[redacted]	10/11/22
Drug Safety & Pharmacovigilance ☐ NA [redacted]	[redacted]	10/10/22
Biometrics ☒ NA [redacted]		

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Approval Signatures		
Name	**Signature**	**Approval Date**
Regulatory Affairs ☐ NA [redacted]	[redacted]	10/17/22
Research ☒ NA		
Clinical Pharmacology ☒ NA		
PRC Chairman ☒ NA		

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Protocol/Protocol Amendment Approval Form

Date circulated for review: 16-Sep-2022

Purpose: Protocol Amendment

Study Number: PCYC-1116-CA

Protocol Version date (DD MMM YYYY): 30 October 2022

☐ **Original**
☒ **Amendment – Version # 4**

Protocol Title: An Open-label Extension Study in Patients 65 Years or Older with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib versus Chlorambucil)

Please indicate that you have reviewed and approve the document listed above by signing and dating below.

Approval Signatures		
Name	**Signature**	**Approval Date**
Clinical Science ☒ NA [redacted]		
Clinical Operations ☒ NA [redacted]		
Drug Safety & Pharmacovigilance ☒ NA [redacted]		
Biometrics ☐ NA [redacted]	[redacted]	10/10/22

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Approval Signatures		
Name	**Signature**	**Approval Date**
Regulatory Affairs ☒ NA [redacted]		
Research ☒ NA		
Clinical Pharmacology ☒ NA		
PRC Chairman ☒ NA		

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Document History

DCR	Rev	Change Description
9848	0	New Form.
10463	1	Addition of Protocol date and version.
21411	2	Reformat signature table to make room for DocuSign electronic signature confirmations.