IST PROTOCOL

IND # 130115

TITLE:	A phase II multicenter single arm study to evaluate the efficacy and safety of single agent Bruton's tyrosine kinase inhibitor, ibrutinib, in patients with relapsed refractory Classical Hodgkin's lymphoma.
PROTOCOL NUMBER:	**2016-033**
STUDY DRUG:	Ibrutinib (PCI-32765)

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DATE FINAL:	25 April 2016

AMENDMENT 1:	1 July 2016
AMENDMENT 2:	5 January 2017
AMENDMENT 3:	11 September 2018
AMENDMENT 4:	14 December 2018
AMENDMENT 5:	27 March 2020
AMENDMENT 6:	23 February 2021
AMENDMENT 7:	**25 October 2022**

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SYNOPSIS

Study Title:	A phase II multicenter single arm study to evaluate the efficacy and safety of single agent Bruton's tyrosine kinase inhibitor, ibrutinib, in patients with relapsed refractory Hodgkin's lymphoma.
Protocol Number:	**2016-033**
Study Phase:	2
Study Duration:	1 year upon completion of accrual
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration.
Objectives:	**Primary Objective:** To determine the antitumor efficacy of single agent ibrutinib as measured by the overall response rate in patients with relapsed/refractory Hodgkin's lymphoma ineligible for; or following ASCT **Secondary Objectives**: To assess duration of tumor control including duration of response (DOR and progression free survival (PFS) To assess the safety and tolerability of 560mg of ibrutinib in HL patients. **Exploratory Objectives:** To assess the mechanism(s) by which ibrutinib may be active in patients with cHL by the correlation of potential biomarkers with clinical outcomes.
Study Design:	Phase II multicenter open label single agent study
Population:	*Relapsed or Refractory Hodgkin's lymphoma* *Ineligible for autologous stem cell transplant* *Or relapse after autologous/allogeneic stem cell transplant*
Centers:	*Multiple*
Inclusion Criteria: *Refer to* Section 4.0 *for the complete and detailed list of inclusion/exclusion criteria.*	*Disease Related* • *Patients with relapsed or refractory Classical HL who have previously received autologous stem cell transplant and/or allogeneic stem cell transplant. Patients must have received prior autologous stem cell transplant at least 12 weeks (3 months) before the first dose of ibrutinib and/or allogeneic stem cell transplant must have been completed at least 6 months prior to the first dose of Ibrutinib.*

	• *or* • *Patients with relapsed or refractory HL who have received at least 2 prior therapies and are not eligible for autologous stem cell transplant due to:* 1. *Inability to achieve a CR or PR prior to transplant* 2. *Age or comorbid conditions* 3. *Inability to collect stem cells* • *Completion of any prior treatment with radiation, chemotherapy, biologics, and/or other investigational agents at least 4 weeks prior to the first dose of ibrutinib. Patients must have completed any prior immunotherapy (e.g., rituximab or PD-1 inhibition) or antibody drug conjugate therapy (e.g. brentuximab vedotin) at least 4 weeks prior to the first dose of ibrutinib.* • *Fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm in minimum dimension by CT scan with contrast, as assessed by the site radiologist.* • *Prior treatment with at least 2 lines of therapy for HL including brentuximab vedotin or individuals who have received at least 2 prior therapies and are not candidates for brentuximab vedotin therapy.* • *Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening and randomization, with the exception of PEGylated G-CSF (pegfilgrastim) and darbopoeitin which require at least 14 days prior to screening and randomization defined as:* • *Absolute neutrophil count >750 cells/mm3 (0.75 x 109/L).* • *Platelet count >50,000 cells/mm3 (50 x 109/L).* • *Hemoglobin >8.0 g/dL.*

	• *Adequate hepatic and renal function defined as:* • *Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN).* • *Estimated Creatinine Clearance ≥30 ml/min (Cockcroft-Gault)***(see appendix 2)** • *Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)* • *PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN.* *Demographic* • *Men and women ≥ 18 years of age.* • *Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.* *Ethical/Other* • *Female subjects who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.* • *Male and female subjects who agree to use highly effective methods of birth control (e.g., condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the period of therapy and for 90 days after the last dose of study drug* • *Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.*
Exclusion Criteria:	*Disease-Related*

	• *Prior allogeneic Stem cell transplant within 6 months.*
	• *Active GVHD or concurrent treatment with immunosuppressive medications as prophylaxis for GVHD*
	• *Previous therapy with BTK inhibition*
	• *Known cerebral/meningeal disease*
	• *Nodular Lymphocyte predominant Hodgkin's Lymphoma*
	Concurrent Conditions:
	• *Concurrent therapy with other systemic anti-neoplastic or investigational agents*
	• *Patients with a known hypersensitivity to any excipient contained in the drug formulation*
	• *History of other malignancies, except:*
	  ◦ *Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.*
	  ◦ *Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.*
	  ◦ *Adequately treated carcinoma in situ without evidence of disease.*
	• *Concurrent systemic immunosuppressant therapy (e.g., cyclosporine A, tacrolimus, etc., or chronic administration [>14 days] of >20 mg/day of prednisone) within 28 days of the first dose of study drug.*
	• *Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.*
	• *Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.*

	• *Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4), grade ≤1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.* • *Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.* • *History of stroke or intracranial hemorrhage within 6 months prior to enrollment.* • *Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.* • *Any uncontrolled active systemic infection.* • *Major surgery within 4 weeks of first dose of study drug.* • *Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.* • *Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to registration.* • *Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.* • *Concomitant use of warfarin or other Vitamin K antagonists.*

	• *Requires treatment with a strong cytochrome P450 (CYP) 3A4/5 inhibitor. (see Appendix 3)* • *Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification* • *Lactating or pregnant.* • *Unwilling or unable to participate in all required study evaluations and procedures.* • *Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).*
Study Treatment:	Ibrutinib 560mg p.o. q.d. until disease progression, unacceptable toxicity or patient/clinician choice to discontinue.
Concomitant Therapy:	Refer to Section 6 for information on concomitant therapy.
Safety Plan:	The Barbara Ann Karmanos Cancer Institute, Data and Safety Monitoring Committee (DSMC), provides the primary oversight of data and safety monitoring for KCI Investigator-initiated trials. In Addition monthly investigator teleconferences will occur to discuss adverse event and safety issues.
Statistical Methods and Data Analysis:	All efficacy analyses will be performed using all evaluable participants. **Primary Efficacy Analysis** A one-sample binomial test will be used to assess efficacy in terms of ORR. The ORR will be reported as a proportion with a one-sided, lower 95% confidence interval. Assuming p0=30%, pA=50%, power=85% and type I error = 10.69% the null hypothesis will be rejected if there are 13 or more ORRs. **Secondary Efficacy Analysis:** DOR will be reported as median and range. Kaplan-Meier estimate of median PFS will be reported with 95% confidence intervals. **Exploratory Efficacy Analysis:**

	The influence of ibrutinib on T cell behavior and antitumor effect will be assessed using a variety of techniques including gene expression and mutational analysis. T cell subset alterations in blood and tumor tissue will be analyzed and PD-1 and PD-2 expression will be evaluated by FISH and IHC. **Safety Analysis:** Frequency of grade 3 or higher adverse events will be tabulated and all grade 1 and 2 adverse events will be collected.
Sample Size Determination	Sample Size Determination A study of 31 evaluable participants was deemed feasible. To accomplish this with an expected not evaluable rate of 12% a total sample population of 35 patients is planned. We specified statistical power of 85% to distinguish a null hypothesis value of 30% against an alternative value of 50% assuming a binomial test of one proportion with a target, one-sided type error of 11%. Under these assumptions the null hypothesis will be rejected if there are 13 or more ORRs among the 31 participants. Accrual Rate, Accrual Duration and Expected Study Duration The expected accrual rate across the 4 institutions is 35 participants per year. Thus it is expected that the duration of accrual will be one year. An additional year is planned for evaluation of the primary, secondary and safety endpoints.

Abbreviations

CRF	case report form (paper or electronic as appropriate for this study)
DSM	Data and Safety Monitoring (DSM) Report
DCF	data clarification form
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eDC	electronic data capture
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
PD	Pharmacodynamic
PK	Pharmacokinetic
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
USP	United States Pharmacopeia
Mos	Months
HRS	Reed Sternberg Cells
cHL	Classical Hodgkin's Lymphoma
KCI	Karmanos Cancer Institute
PCYC	Pharmacyclics

OBJECTIVES

Primary Objective

To determine whether the antitumor efficacy of single agent ibrutinib as measured by the overall response rate in patients with relapsed/refractory Hodgkin's lymphoma ineligible for; or following ASCT is sufficient to justify further study.

Secondary Objective

To assess duration of tumor control including duration of response (DOR and progression free survival (PFS).

To assess the safety and tolerability of 560mg of ibrutinib in cHL patients.

Safety Objectives

To assess the safety and tolerability of 560mg of ibrutinib in cHL patients.

Exploratory Objectives

To assess the mechanism(s) by which ibrutinib may be active in patients with cHL by the correlation of potential biomarkers with clinical outcomes

Background

1. INTRODUCTION

Ibrutinib (also referred to as PCI-32765 or JNJ 54179060) is a first-in-class potent, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently being co-developed by Pharmacyclics LLC and Janssen Research & Development, LLC (JRD). It has demonstrated single-agent activity in several B-cell lymphomas, including relapsed mantle cell lymphoma (MCL), with an acceptable safety profile.

For the most comprehensive nonclinical and clinical information regarding ibrutinib, refer to the latest version of the ibrutinib (PCI-32765) Investigator's Brochure and Addenda.

1.1. Disease/Histology

Classical Hodgkin's Lymphoma (cHL) is a malignancy of mature (post germinal center) B-lymphocytes that afflicts almost 20,000 individuals annually in North America and Europe alone. Uniquely, the malignant Reed Sternberg (RS) cell in cHL comprises only a fraction of the tumor mass in pathologic lymph nodes (LN) with the majority of the tumor composed of activated T and B lymphocytes and a variety of other hematopoietic elements. While the majority of patients diagnosed with cHL are cured with multi-agent chemotherapy, 15 % of patients are refractory to conventional chemotherapy and almost half of patients with high-risk disease relapse.[1] For these patients few effective therapeutic options exist. Only one agent has been approved in the last 30 years for relapsed HL and novel therapies are needed.[2]

1.1.1. Treatment Options

Current initial therapy for the treatment of HL includes adriamycin, (doxorubicin) bleomycin, vinblastine and dacarbazine (ABVD). In patients who relapse options include salvage chemotherapy followed by autologous stem cell transplant (ASCT) which results in long term disease free progression rates of 50%.[1] Other options include brentuximab vedotin an antibody drug conjugate which has shown significant single agent activity in HL and is approved after ASCT or failure of 2 prior lines of therapy.[2]

1.1.2. Role of BTK in Disease/Histology

Bruton's Tyrosine Kinase (BTK) is a member of the TEC family and plays a central role in B-cell signaling, activation, proliferation and differentiation. BTK is expressed in normal B-cells, myeloid cells and macrophages. In addition to activation by the B-cell receptor, several studies have shown that BTK has been associated with PI3K, mTOR, FAS and NF-κB signaling. Furthermore, BTK can be activated by CD40 ligand binding, chemokines such as IL-6 and activation of toll like receptor (TLR) pathways.[5,6] Many of these pathways are also known to play important roles in the pathologic behavior of HL cells. In particular, CD 40, mTOR NF-kB and toll like receptor pathways have been identified as targets for possible therapeutic intervention in cHL.[1,7]

Recent data has also suggested that T cell cytotoxicity and immune surveillance is important in the pathogenesis of cHL. This may be particularly true in patients with high copy numbers of chromosome 9p24.1 as determined by fluorescence in situ hybridization.[11] Novel therapies have taken advantage of this by stimulating native T cells in this population with excellent results in relapsed cHL patients.[11] Ibrutinib has shown the ability to potentially subvert Th2 immunity potentiating Th1 based immune responses through inhibition of ITK.[12] This may in turn enhance a Th1 dominant cytotoxic immune response against the malignant clone in cHL.

Lastly, as the RS cell comprises only a fraction of the tumor mass in patients with HL, the tumor microenvironment is also likely to be of vital importance. It has been hypothesized that activated B-cells, macrophages and other hematopoietic elements provide anti-apoptotic and survival signals necessary for the survival of the malignant RS population.[7] Therapies directed at the tumor microenvironment have previously demonstrated significant and durable responses in highly refractory cHL patients.[8,10] BTK over activity has been associated with chemokine related homing, adhesion and migration by inhibition of CXCR4/5 and CXCL 12/13 in B cells.[3,4] Consequently interruption of the microenvironment by BTK inhibition may result in anti-tumor effect.

1.2. Investigational Product Name and Description

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and

selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. Ibrutinib (IMBRUVICA®) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of: 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based on overall response rate, 2) chronic lymphocytic leukemia (CLL) including CLL with a deletion of the short arm of chromosome 17 (del17p) or a *TP53* mutation, and 3) in patients with Waldenstrom's macroglobulinemia. Ibrutinib is currently under investigation in various indications.

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

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

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite 2000).

Data from Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post dose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

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

1.3. Summary of Nonclinical Data

For the most comprehensive nonclinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

In HL cell lines H2 were grown in vitro and incubated with increasing concentrations of ibrutinib for 72 hrs. Incubation of the cell line with ibrutinib resulted in a significant reduction in viability by trypan blue analysis in a dose dependent manner. Additionally, apoptotic studies confirmed the induction of cell death by BTK inhibition with ibrutinib in both annexin V-FITC assays and histone DNA ELISA studies. Lastly, caspase-3 and PARP cleavage was demonstrated in this cell line. (Azmi A, Ramchandren R unpublished data)

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 B-cell receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

For more detailed and comprehensive information regarding nonclinical pharmacology, refer to the current Investigator's Brochure.

1.3.1. Toxicology

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

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

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the dose of 420 and 560 mg daily, respectively.

1.3.1.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

1.4. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

1.4.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose 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.

1.5. Summary of Clinical Safety

Integrated safety data from a total of 1,523 subjects with B-cell malignancies treated with ibrutinib monotherapy in 17 studies that have completed primary analysis or final analysis included in the CSR as of the 31 July 2017 cutoff date for the current IB update in B-cell malignancies are summarized below.

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

Most frequently reported TEAEs >10% [a]	Most frequently reported Grade 3 or 4 TEAEs >2% [a]	Most frequently reported Serious TEAEs >1% [b]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Pyrexia
Cough	Anemia	Febrile neutropenia
Pyrexia	Hypertension	Sepsis
Anemia	Diarrhea	Cellulitis
Upper respiratory tract infection	Atrial fibrillation	Pleural effusion
Neutropenia	Fatigue	Dyspnoea
Oedema peripheral	Neutrophil count decreased	Urinary tract infection
Thrombocytopenia	Febrile Neutropenia	Lung infection
Muscle spasms	Hyponatraemia	Abdominal pain
Constipation	Hypokalaemia	Acute kidney injury
Arthralgia		Anemia
Vomiting		Respiratory failure
Decrease appetite		
Dyspnoea		
Headache		
Pneumonia		
Rash		
Hypertension		
Abdominal pain		
Back pain		
Contusion		

Dizziness

[a] Source is Table 5 of IB (v11), [b] Source is Table 6 of IB (v11)

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

1.5.1. Risks

Long-term safety
The long-term safety data over 4 years from 1,177 subjects (CLL/SLL n = 807 and MCL n = 370) treated with ibrutinib were analyzed. The median duration of treatment for CLL/SLL was 45 months with 70% and 40% of subjects receiving treatment for more than 2 years and 4 years. The median duration of treatment for MCL was 11 months with 31% and 14% of subjects receiving treatment for more than 2 years and 4 years. The overall known safety profile of ibrutinib-exposed subjects remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2-3), and 8% (year 3-4). The incidence for the 4-year period was 10%.

Bleeding-related events

There have been reports of bleeding events in subjects treated with ibrutinib both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed, refer to Section 6.2.4. Use of either anticoagulant or antiplatelet agents comcomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs or symptoms of bleeding. See Section 6.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements.

Supplements such as fish oil and vitamin E preparations should be avoided.

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 6.3 for guidance on ibrutinib management with surgeries or procedures.

Subjects with congenital bleeding diathesis have not been studied.

Cardiac arrhythmias
Atrial fibrillation, atrial flutter, 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 persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines. For cardiac arrythmia which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.4.1.5).

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Monitor complete blood counts monthly.

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 and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.4.1.5).

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (reference Section **Error! Reference source not found.**). 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 signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

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.

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.

For subject and ibrutinib management guidance, refer to Section 5.3.1.5.

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. Consider temporarily holding ibrutinib. Subjects should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated. For subject and ibrutinib management guidance, refer to Section 5.3.1.5.

Lymphocytosis

Upon initiation of single agent treatment with ibrutinib, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count >5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL/SLL. This effect has also been observed in some subjects (35%) with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month 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 (range, 0.1 to 104 weeks).

When ibrutinib was administered in combination with BR or with obinutuzumab in subjects with CLL/SLL, lymphocytosis was infrequent (7% with ibrutinib + BR versus 6% with placebo + BR and 7% with ibrutinib + obinutuzumab versus 1% with chlorambucil + obinutuzumab). Lymphocytosis was not observed in subjects with WM treated with ibrutinib.

Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

Interstitial lung disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt

ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.3.1.5).

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.

Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

1.6. Study Rationale

Despite the curability of HL in patients with ABVD, it remains a serious and fatal malignancy in patients who relapse after ASCT or cannot undergo intensive therapy. Due to the young age of this population (median 30 yrs.) the number of years of life lost is substantial with a median overall survival (OS) of only 3 years if relapse occurs after stem cell transplant[1]. In this population there is an unmet medical need, particularly for those patients who relapse or become refractory to treatment. The expected survival is progressively shorter with each subsequent relapse. Brentuximab vedotin is the only FDA approved agent in the US for patients who have received at least 2 prior therapies. However less than 40% of patients achieve a complete remission (CR) with this therapy and eventually all patients who receive this therapy will relapse with no other approved therapeutic options. As an oral daily treatment, ibrutinib may offer a treatment option to this otherwise terminal patient population who are without alternative approved treatment options. Based on the activity of ibrutinib in other B cell malignancies, the well-defined toxicity profile and encouraging pre-clinical data, we hypothesize that BTK inhibition with ibrutinib may have clinical benefit in patients with Hodgkin's lymphoma with a novel mechanism of action.

1.7 Exploratory Rationale

Gene expression profiling and mutational analysis of laser micro dissected HRS cells will be performed to evaluate genes of interest. This will be performed on archival tissue blocks that must be submitted as described in the lab manual. Whenever possible the most recent biopsy sample must be sent for evaluation. If archival tissue is not available a fresh biopsy must be

performed prior to treatment with study drug. An excisional biopsy is preferred in all instances however, when an excisional biopsy is not possible a core biopsy will be allowed. If core biopsy is utilized then 4-6 cores must be provided for analysis to ensure adequate sample. In those patients who progress or do not respond to therapy, end of study (EOT) testing includes and optional, highly recommended tumor biopsy for assessment. In this instance excisional or core biopsy will be acceptable.

To assess ibrutinib's influence on T cell behavior and antitumor effect, serial serum samples pre and post therapy will be assessed for Th1 ((IFN-g) and Th2 cytokines (IL-10, IL-4 and IL-13) at 4 distinct time points (pre-dose, cycle 1 day 2 , day 15, and day 28) . The cytokine profiles pre and post therapy with ibrutinib will be compared to assess modifications in T cell subsets due to ibrutinib therapy.[12] In addition post treatment T cell populations will be compared with tumor microenvironment populations.

HL has shown sensitivity to T cell immune based anti-neoplastic therapy.[11] A potential predictor of immune based therapy may be the presence of overexpression of the PDL1 and PDL2 proteins. Due to the potential of ibrutinib to alternative immunity through T cell subsets correlating responses to T cell alterations and malignant overexpression of PDL1 and PDL2 may be beneficial. Consequently, archived tissue will be evaluated by three probe FISH assay for relative copy gain or polysomy of chromosome 9p.11. This data will then be correlated with clinical activity of ibrutinib in cHL.

Therefore **whenever possible** a biopsy (preferably a lymph node excision) performed after the most recent therapy is **highly recommended**. In the event an excisional biopsy is not possible then a core tissue biopsy is acceptable with a **minimum of 4 cores**. In the event a biopsy cannot be obtained upon the completion of their most recent therapy, an archival tissue block must be submitted for analysis. The archival tissue must be from the most recent biopsy with adequate specimen.

2. STUDY OBJECTIVE

2.1. Primary Objective

To determine the antitumor efficacy of single agent ibrutinib as measured by the overall response rate in patients with relapsed/refractory Hodgkin's lymphoma ineligible for, or post ASCT

2.2. Secondary Objective(s)

- To assess duration of tumor control including duration of response (DOR) and progression free survival (PFS)

- To assess the safety and tolerability of 560mg of ibrutinib in HL patients.

2.3. Exploratory Objective(s)

- To assess the mechanism(s) by which ibrutinib may be active in patients with cHL by the correlation of potential biomarkers with clinical outcomes.

3. STUDY DESIGN

3.1. Overview of Study Design

This is a multicenter, single-arm Phase 2 study to evaluate the efficacy and safety of single-agent ibrutinib in subjects with HL who have received at least 2 prior chemotherapy regimens and are ineligible for ASCT or have progressed after ASCT. Approximately 35 eligible subjects will be enrolled to have 31 evaluable subjects for overall response to treatment.

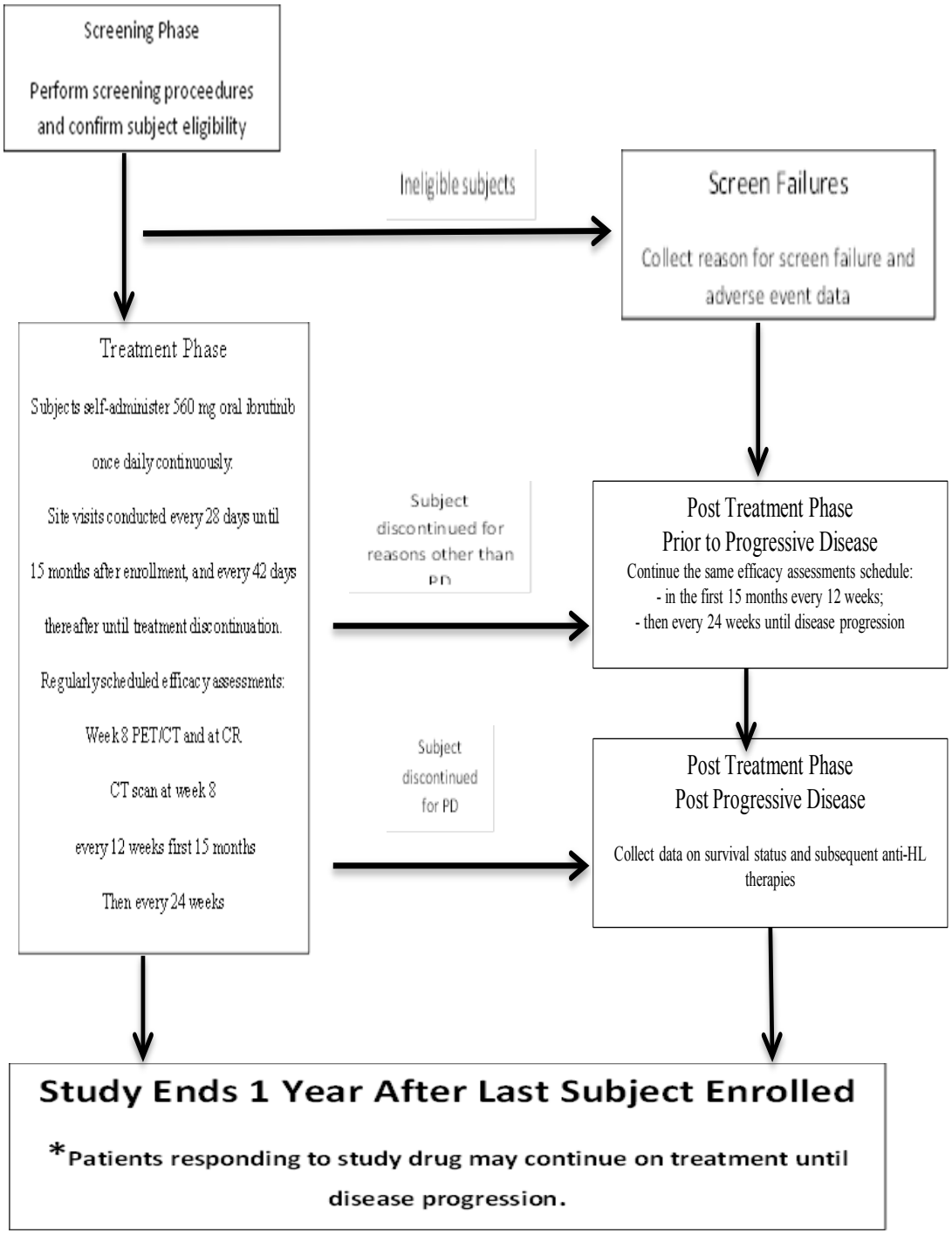
Subject participation will include a Screening Phase, a Treatment Phase, and a Posttreatment Phase **(Figure 1).** The Screening Phase will be up to 28 days and include a computed tomography (CT), or MRI scan and a positron emission tomography (PET) scan, prior to first dose. A formalin-fixed paraffin embedded tumor (FFPE) block must be sent to the central laboratory for confirmation of HL and biomarker analysis diagnosis. However, prior to enrollment, a report from the local laboratory that contains relevant data documenting HL diagnosis is acceptable.

The Treatment Phase will extend from the administration of the first dose of ibrutinib until the completion of the End of Treatment Visit. Subjects will receive 560 mg oral ibrutinib once daily on a 28-day cycle until disease progression (or relapse if the subject achieved a CR) or occurrence of unacceptable toxicity, whichever occurs first. Regularly scheduled disease assessments are required throughout the Treatment Phase to assess Efficacy **(See appendix 1).** PET imaging is required to document complete remission (CR). PET imaging is to be performed after 2 cycles of therapy, at the time of maximal tumor reduction (e.g., CR or 2 consecutive CT scans showing no further tumor reduction), relapse from CR, and at suspected disease progression if new lesion was detected on CT. Tumor (from lymph node biopsies or diagnostic biopsy tissue collected during screening), blood, and/or bone marrow aspirate/ biopsy will be evaluated to identify markers predictive of response to ibrutinib. Bone marrow biopsy will be used to confirm CR if marrow involvement is present at baseline. During the study, safety evaluations will include adverse event monitoring, physical exams (including changes to concomitant medications and assessment of lymphoma B-symptoms), and clinical laboratory parameters **(See Appendix 1)**. Subjects will be provided a diary card to record study drug intake **(See Appendix 6)**. At each site visit, site personnel will check ibrutinib daily dosing and evaluate the subject for toxicity; doses can be held or reduced based on the severity of and the recovery from a previous toxicity. Dose re-escalation will ONLY be allowed after discussion with medical monitor, otherwise no dose escalation will be permitted. Subjects who discontinue from treatment will enter the Posttreatment Phase. Regularly scheduled disease assessments are required during the Posttreatment Phase for subjects who discontinue treatment prior to disease

progression, until the clinical cutoff. During the Posttreatment Phase, data on PFS, overall survival, and subsequent anti-HL therapies will be collected from all subjects except those who explicitly withdraw consent for further follow-up. It is imperative that survival status be assessed and that the date of death is documented for each treated subject.

Study Schema (include Figure)

3.2.



3.3. Study Design Rationale

3.3.1. Study Population and Treatment

Patients with HL who have relapsed after autologous and/or allogeneic stem cell transplant or have relapsed after a minimum 2 prior lines of therapy and are transplant ineligible due to: inability to tolerate transplant as determined by their treating physician, inability to achieve a complete response (CR), comorbidities or age.

Ibrutinib will be prescribed at a dose of 560mg given orally daily. Patients will be assessed weekly during the initial cycle for toxicity and adverse event reporting. Dose interruptions and modifications will occur based on standard ibrutinib prescribing guidelines in NHL **(see 5.4.1.5)**. Treatment will continue on study until disease progression, patient/investigator discontinuation or unacceptable toxicity.

3.3.2. Dose Selection

Data from Study PCYC-04753 showed that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post dose at dose levels ≥2.5 mg/kg. In study PCYC-04753, greater than 85% of patients who received dosages ≥2.5 mg/kg/day had Day 1 AUC0-24 values ≥160 ng·h/mL. The analysis of pharmacokinetic and pharmacodynamic profiles showed that BTK active-site occupancy was saturated or near saturated (>95%) at AUC values of ≥160 ng·h/mL.[15] In study PCYC-1104-CA where ibrutinib was administered to relapsed/refractory MCL patients as a fixed dosage of 560 mg/day, 96% of the patients retained steady-state ibrutinib AUC values >160 ng·h/mL.[16] This result indicates that the vast majority of patients who received a dose of 560 mg/day will achieve exposures yielding full BTK active-site occupancy. An interim analysis has confirmed a high rate of response (approximately 70%) with this dose in relapsed or refractory MCL with an acceptable toxicity profile. Based on these data, the oral daily 560 mg dose has been selected for this study. Based on these data, and because of the modest and acceptable toxicity profile of ibrutinib, subjects in this study will be treated until progressive disease or occurrence of unacceptable toxicity, whichever comes first. Patients deriving benefit as deemed by the treating physician may continue on study drug until progression, or unacceptable toxicity.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all of the following inclusion criteria.

Disease Related

1. Patients with relapsed or refractory classical HL who have previously received autologous stem cell transplant and/or allogeneic stem cell transplant. Patients must have received prior autologous stem cell transplant at least 12 weeks (3 months) before the first dose of ibrutinib and/or allogeneic stem cell transplant must have been completed at least 6 months prior to the first dose of Ibrutinib.

or

Patients with relapsed or refractory HL who have failed at least 2 lines of prior therapy and are not eligible for autologous stem cell transplant due to:

   a. Inability to achieve a CR or PR prior to transplant

   b. Age or comorbid conditions

   c. Inability to collect stem cells

2. Completion of any prior treatment with radiation, chemotherapy, biologics, and/or other investigational agents at least 4 weeks prior to the first dose of ibrutinib. Patients must have completed any prior immunotherapy (e.g., rituximab or PD-1 inhibition) or antibody drug conjugate therapy (e.g. brentuximab vedotin) at least 4 weeks prior to the first dose of ibrutinib in the absence of clear disease progression.

3. Prior treatment with at least 2 lines of therapy for HL including brentuximab vedotin. In those patients who cannot receive brentuximab vedotin, treatment with 2 prior therapeutic regimens is sufficient.

4. Fluorodeoxyglucose (FDG)-avid disease by PET and measurable disease of at least 1.5 cm in minimum dimension by CT scan with contrast, as assessed by the site radiologist.

PROTOCOL SPECIFIC

Laboratory

1. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening and randomization, with the exception of PEGylated G-CSF (pegfilgrastim) and darbopoeitin which require at least 14 days prior to screening and randomization defined as:
   - Absolute neutrophil count >750 cells/mm^3 (0.75 x 10^9/L).
   - Platelet count >50,000 cells/mm^3 (50 x 10^9/L).
   - Hemoglobin >8.0 g/dL.
2. Adequate hepatic and renal function defined as:

- Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN).
- Estimated Creatinine Clearance ≥30 ml/min (Cockcroft-Gault)
- Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)

3. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN.

Demographic

4. Men and women ≥ 18 years of age.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

Ethical/Other

6. Female subjects who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.
7. Male and female subjects who agree to use highly effective methods of birth control (e.g., condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the period of therapy and for 90 days after the last dose of study drug
8. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

Disease-Related

1. Prior allogeneic Stem cell transplant within 6 months.
2. Active GVHD or concurrent treatment with immunosuppressive medications as prophylaxis for GVHD
3. Previous therapy with BTK inhibition
4. Known cerebral/meningeal disease
5. Nodular lymphocyte predominant Hodgkin's Lymphoma subtype

PROTOCOL SPECIFIC

Concurrent Conditions

1. Concurrent therapy with other systemic anti-neoplastic or investigational agents
2. Patients with a known hypersensitivity to any excipient contained in the drug formulation
3. History of other malignancies, except:
    - Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    - Adequately treated carcinoma in situ without evidence of disease.
4. Concurrent systemic immunosuppressant therapy (e.g., cyclosporine A, tacrolimus, etc., or chronic administration [>14 days] of >20 mg/day of prednisone) within 28 days of the first dose of study drug.
5. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
6. Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.
7. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4), grade ≤1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
8. Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.
9. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
10. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). *Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.*
11. Any uncontrolled active systemic infection.
12. Major surgery within 4 weeks of first dose of study drug.
13. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
14. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
15. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
16. Concomitant use of warfarin or other Vitamin K antagonists.

17. Requires treatment with a strong cytochrome P450 (CYP) 3A4/5 inhibitor (see Appendix 3).
18. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix 7).
19. Lactating or pregnant.
20. Unwilling or unable to participate in all required study evaluations and procedures.
21. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation. During the study, subjects should avoid consuming food and beverages containing grapefruit or Seville oranges as these contain certain ingredients that inhibit CYP3A4/5 enzymes.

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

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

5. TREATMENT OF SUBJECTS

5.1. Treatment Registration

Consent must be signed before any study specific procedures are performed. Once a patient is consented, the site must email/fax a copy of the consent and the patient pre-registration form to the lead personnel at Karmanos Cancer Institute within 24 hours. Each patient will be assigned a unique identification number upon consenting and registration approval by the KCI lead coordinator which will be used to track all correlative shipments and study drug dispensation. The subject must also be entered into Oncore by the participating site within 24 hours of consent. Training for Oncore will be provided during site initiation. The participating site will provide

the registration form, eligibility checklist and all source documents to support patient eligibility to Karmanos and sites must receive approval from Karmanos prior to initiating study treatment. All subjects will receive the same treatment regimen, single-agent Ibrutinib.

5.1.1. Study treatment

For the purposes of this study, 'study drug' refers to ibrutinib. Treatment will be administered until disease progression or relapse after CR, or occurrence of unacceptable toxicity, whichever comes first. Patients deriving benefit as deemed by the treating physician may continue on study drug until progression, or unacceptable toxicity.

5.2. Route and schedule

Ibrutinib is to be taken in the morning (around the same time each day) with approximately 8 ounces (240 mL) of water. All 4 capsules should be taken at the same time. The capsules should be swallowed whole and should not be opened, broken, or chewed. The daily self-administered home treatment is to be continuous (without interruption). Subjects should avoid consuming food and beverages containing grapefruit or Seville oranges for the duration of the study due to CYP 3A4/5 inhibition. Subject should refrain from taking the study drug on the morning of study visits until seen at the site.

If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose. Variations in dosing are not considered unsafe if more than 12 hrs of time are provided between doses. If doses occur within 12 hours of each other this will be considered a minor deviation. During the first 15 months, study drug will be dispensed at the beginning of each 28-day cycle. Subjects will be provided with 2 days overage each time study drug is dispensed to allow for delayed return visits. Unused ibrutinib, dispensed during previous visits, must be returned and drug accountability records updated. Returned capsules must be discarded and cannot be re-used in this study or outside the study. Study staff will instruct subjects on how to store ibrutinib for at-home use as indicated for this protocol. After 15 months of treatment, patient site visits may be conducted every 56 days. Sufficient drug supply until next visit will be dispensed.

5.3. Study Medication

Subjects will receive 560 mg oral ibrutinib once per day, continuously during a 28 day treatment cycle. Each capsule contains 140 mg of ibrutinib. Subjects will be instructed to take 4 capsules for a dose of 560 mg.

5.3.1. Ibrutinib

5.3.1.1. Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drugs will be dispensed in child-resistant packaging. Study drug labels will contain information to meet the applicable regulatory requirements.

Drug Storage: The labeled storage condition for ibrutinib is between 15-25°C (59-77°F), with excursions permitted up to 30°C. Total cumulative excursions between 25°C and 30°C must not exceed 12 months. Temperatures lower than 15°C or greater than 30°C must be reported to Pharmacyclics for evaluation of impact on product quality. In storage areas where the temperature can exceed or fall below the required storage conditions (e.g., air conditioning, heating), measures must be in place to maintain the required temperature. Ibrutinib should be kept away from direct sunlight.

Temperature conditions during on-site storage of study drug must be closely monitored and recorded (e.g., temperature logs, or data, charts or graphs from temperature monitoring equipment or devices). All monitoring equipment must be calibrated in accordance with the manufacturer's recommendations. All documentation/data of the storage temperature must be retained in accordance with the records retention policy outlined in the Protocol and applicable legal and regulatory requirements.

The storage temperature documentation must identify or link to (e.g., through the serial number or unique identifier) the thermometer or temperature monitoring equipment and, if applicable the refrigerator/freezer. These logs must be made available to the monitors for review at routine interim monitoring visits.

5.3.1.2. Dose and Administration

Ibrutinib 560 mg (4 x 140-mg capsules) is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study **(Appendix 3)**.

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

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 5.4.1.3) updated at each visit. Returned capsules must not be re-dispensed to anyone.

5.3.1.3. Drug Accountability

The site specific investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. The subject or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of per institution's protocol. Site staff must not combine contents of the study drug containers. Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the lead investigators. When study drug supplies are destroyed on site per institutional protocol, a tablet count and disposal method should be documented on the drug return form. Study drug should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug (ibrutinib) must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the investigating sponsor.

The investigator will be provided with a drug accountability diary to be provided to patients beginning therapy prior to or on day one of treatment. Patients must be instructed to document ibrutinib usage per the diary requirements. The drug diary should be reviewed by the study staff prior to drug dispensation for every cycle. Discrepancies between the returned drug accountability and diary must be evaluated at the beginning of each cycle.

5.3.1.4. 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 ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment. Refer to Section 10 for further information regarding AE reporting.

5.3.1.5. Dose Modification for Adverse Reactions

The dose of study drug should be modified according to the dose modification guidelines in Table 1 if any of the following toxicities occur:

- Grade 4 ANC (<500/µL) for more than 7 days. See Section 6 for instructions regarding the use of growth factor support.
- Grade 3 thrombocytopenia (<50,000/µL) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia (<25,000/µL).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.4).

Table 1. Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (i.e. 420 mg/day for 560 mg /day dose)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (i.e. 280 mg/day for 420 mg /day dose)
Fourth	Discontinue study drug

A high number of circulating malignant cells (>400,000/mcL) may confer increased risk of leukostasis; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and principal investigator should be contacted.

5.4. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant chronic hepatic impairment at the time of screening (Child- Pugh class C) are excluded from study participation. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. Refer to Appendix D for Child-Pugh classification. Please refer to Table 2

for dose modifications due to hepatic impairment. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix 7).

Table 2: Dose Modification due to Hepatic Impairment

	Child Pugh class A (Mild hepatic impairment)*		**Child Pugh Class B (Moderate hepatic impairment)****		**Child Pugh class C (Severe hepatic impairment)**
	Ongoing at time of enrollment	Develops during study	Ongoing at time of enrollment	Develops during study	Develops during study
Ibrutinib Dose (daily)	280 mg	280mg	140 mg	140 mg	Hold until improves to moderate [Class B] or better)

* If further reduction is needed due to non-hepatic toxicity, dose may be reduced to 140 mg. In the event that additional reduction is needed, ibrutinib should be held for non-hepatic toxicity until resolution.

** If further reduction is needed due to non-hepatic toxicity, ibrutinib should be held until resolution.

5.5. Criteria for Permanent Discontinuation of Study Drug

Study drug may be held for a maximum of 28 consecutive days. Study treatment should be permanently discontinued in the event of a toxicity lasting >28 days. Once the ibrutinib dose is reduced it cannot be re-escalated without a discussion with the medical monitors (Dr. Modi or Dr. Ramchandren).

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1. 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) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006) beginning cycle two day one of therapy. Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted.

Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

Standard supportive care therapies (e.g., antiemetics, loperamide) needed for the management of symptoms are permitted, as clinically indicated, other than anticancer treatment.

6.2. Medications to be Used with Caution

6.2.1. CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib with drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure. Dose adjustment of ibrutinib due to concomitant use of CYP3A inhibitors should follow Table 3.

Table 3. Dose Modification Guidance for CYP3A Inhibitors/Inducers

Patient Population	**Co-administered Drug**	**Recommended Ibrutinib Dose for the Duration of the Inhibitor Use[a]**
B-Cell Malignancies	Mild CYP3A inhibitors	420 mg or 560 mg once daily per indication. No dose adjustment required.
	Moderate CYP3A inhibitors	280 mg once daily.
	Voriconazole Posaconazole at doses less than or equal to suspension 200 mg BID	140 mg once daily.
	Other strong CYP3A inhibitors Posaconazole at higher doses[b]	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

a. Monitor for adverse reactions to IMBRUVICA and interrupt or modify dose as recommended (see Dosage and Administration).

b. Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

After discontinuation of a CYP3A inhibitor, resume previous dose of ibrutinib.

Avoid concomitant use of systemic 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 3. A comprehensive list of inhibitors, inducers, and substrates may be found at

http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

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

6.2.2. 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 (with an IC_{50} of 2.15 μg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. 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.

6.2.3. QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered

For a list of potential medications which may prolong the QT interval please review the following link. If there are additional questions/concerns contact the P.I. Dr. Modi or Dr. Ramchandren.

www.rettsyndrome.eu/wp-content/uploads/2015/10/CombinedList.pdf

6.2.4 Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. 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 subjects treated with ibrutinib. 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 6.3).

6.3. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment.

Corticosteroids for the treatment of the underlying disease are prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100mg of prednisone or its equivalent are prohibited.

Erythropoietic growth factors (eg, erythropoietin) and neutrophil growth factors (eg, filgrastim and peg-filgrastim) are also prohibited during the initial cycle (28 days) of treatment

6.4 Guidelines for Ibrutinib Management with Surgeries or Procedure

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 subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, skin or needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib.

6.4.2. 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 serosanguinous drainage or the need for drainage tubes.

7. STUDY EVALUATIONS

7.1 Description of Procedures

The study is divided into 3 phases: a Screening Phase, a Treatment Phase, and a Post treatment Phase. Screening occurs from the time of informed consent up to commencement of therapy on cycle 1 day 1. Treatment includes the time frame from commencement of therapy including the end of treatment visit. The post treatment phase includes the time from end of treatment until progression, death or next therapy. During the Post treatment Phase, subjects will be followed for survival and subsequent anti-HL therapy until death, withdrawal of consent, confirmed lost to follow-up, or the end of study, whichever occurs first.

7.1.1. Assessments

- **Screening phase**
  - All patients must sign an informed consent prior to any study related procedures listed below with the exception of CT or PET imaging which can be performed prior to informed consent if done within 28 days of Day 1 of therapy.

- Screening procedures will be performed up to 28 days before first dose of study drug. Subjects must satisfy all of the inclusion and none of the exclusion criteria listed in Section 4.1 and Section 4.2, respectively, before receiving the first dose of study drug. The results of laboratory tests noted in the inclusion criteria must be within the limits specified prior to the first dose of study drug. Testing can be repeated for this purpose. The last result obtained prior to start of study treatment will be used to determine eligibility
- During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed (Appendix 1). A complete medical history and physical exam (including concomitant medications, vital signs, height, and weight) with baseline evaluation of lymphoma B-symptoms, adverse events and ECOG performance status **(See appendix 2)** will be conducted.
- 12 lead ECG
- All subjects must undergo a whole body FDG-PET scan and CT scan with contrast. Evaluation of other sites of disease, as relevant, may be performed. In instances where contrast cannot be utilized a discussion with the principal investigator is necessary.
- Laboratory studies including CBC with differential, Serum chemistries, hepatitis serologies, coagulation panels (**See Appendix 1)**
- Correlative biomarker analysis MUST be drawn prior to dose on cycle 1 day 1 of therapy (**See Lab Manual)**
- **A fresh tissue biopsy (excisional lymph node biopsy) is highly recommended for correlative analysis. In instances where an excisional lymph node biopsy is not obtainable, core needle biopsy (4 cores minimum) is recommended.**
- If fresh tumor biopsy is unobtainable, a formalin-fixed paraffin embedded (FFPE) tumor block must be submitted for correlative analysis. (**See Lab Manual**) For screening, a report confirming the diagnosis of Hodgkin's lymphoma is required.
- Subjects must initiate ibrutinib treatment within 28 days of the start of the screening phase

- **Treatment Phase**
  - Throughout the Treatment Phase, the investigator will assess subject response to therapy using efficacy measurements and disease response criteria. Subjects will be monitored for safety, and adverse event information will be collected using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. Dose modifications will be made as required according to dose-modification rules (Section 5.4). The frequency of study procedures and assessment to be conducted during the Treatment Phase are outlined in Appendix 1. However, clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated
  - During each Day one of therapy a symptom-directed physical exam (including lymphoma B-symptoms and performance status will be conducted and the results of all laboratory tests will be reviewed. Adverse events and changes to concomitant medications will be recorded (**see Section 6 for concomitant medications**). Subjects will be evaluated throughout the Treatment Phase for possible toxicities, and modifications in dosing will be made as required according to the criteria in Section

3. The investigator will assess subject response to therapy using the efficacy measurements and disease response criteria according to the schedule described the study calendar **(See Appendix 1 notation g and i)**. For subjects who remain on study treatment beyond 15 months from the date of enrollment, site visits may be conducted every 56 days.

- Subjects will be issued diary cards to record study drug dosing. Instructions for proper self-administration and study drug storage conditions will be provided. Precaution associated with the use of study drug and prohibited concomitant medications will be reviewed. The investigator or designated study research staff will review the study diary at the beginning of each cycle and provide additional instruction to re-educate any patient who has not followed the study treatment schedule. Patients on study should refrain from taking the study drug on the morning of study visits designated for commencement of a new cycle until seen at the site. When all evaluations have been completed, and it has been determined that the subject can continue treatment, ibrutinib capsules for 1 cycle of treatment will be dispensed.
- Treatment will continue until progressive disease or unacceptable toxicity occurs. If progressive disease is diagnosed the subject will discontinue study drug, complete the End of Treatment Visit within 30 days, and enter the Post treatment Phase.
- To assess ibrutinib's influence on T cell behavior and antitumor effect, serial serum samples pre and post therapy will be assessed for Th1 ((IFN-g) and Th2 cytokines (IL-10, IL-4 and IL-13) at 4 distinct time points (pre-dose cycle 1 day one, cycle 1 day 2 , cycle 1 day 15) , and cycle 2 day 1 **(See Appendix 1)**. All assessments will occur prior to dosing that day. **Patients must be instructed not to swallow study drug prior to biomarker evaluation on cycle 1 day 1, cycle 1 day 2, cycle 1 day 15, and cycle 2 day 1.**
- An End of Treatment Visit will be scheduled within 30 days after the last dose of study drug for all subjects, including those discontinuing treatment for any reason, except for those lost to follow-up, death, or withdrawal of consent for study participation. Subjects who discontinued from treatment (due to progression, adverse event, or other reasons) and enter the Posttreatment Phase should have the End of Treatment Visit completed before starting any subsequent anti-HL treatment. If a subject is unable to return to the site for the End of Treatment Visit, the subject should be contacted to collect adverse events that occur within 30 days after the last dose of study drug.

- **Follow Up Phase**
  - The Posttreatment Phase is the time between the End of Treatment Visit and end of study participation or the end of study. The clinical cutoff for primary analysis will occur approximately 1 year after the last subject is enrolled. Investigators will be informed of the timing of the clinical cutoff. It is imperative that the regularly scheduled disease assessments (clinical and radiographic) are performed throughout the Posttreatment Phase for subjects who discontinue treatment prior to disease progression, as outlined in Section 7.3.1 Evidence of clinical relapse according to the Revised Response Criteria for Malignant Lymphoma is to be documented at the time at which it is first detected. During this period, assessments will be performed until

disease progression, death or study end, whichever comes first. Subjects off treatment will be contacted every 9 weeks to obtain data on subsequent anti-HL therapies (including treatment regimen, start date, end date, and best response to subsequent therapy) and survival status. If the information on subsequent anti-HL therapies and survival status is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the CRF.

7.1.2. Pharmacokinetics/Biomarkers

- To assess ibrutinib's influence on T cell behavior and antitumor effect, serial serum samples pre and post therapy will be assessed for Th1 ((IFN-g) and Th2 cytokines (IL-10, IL-4 and IL-13) at 4 distinct time points (pre-dose cycle 1 day one, pre-dose cycle 1 day 2 , pre-dose cycle 1 day 15) , and pre-dose cycle 2 day 1 (**See Appendix 1)**. All assessments will occur prior to dosing that day.

7.2.0 Efficacy Evaluations

The investigator will perform tests that will allow evaluation of response to therapy according to the Revised Response Criteria for Malignant Lymphoma.[13] An evaluable patient will be defined as "any patient receiving study drug for > 1 cycle and having completed at least one radiographic (CT with contrast or PET) evaluation. Patients missing > 25% (14 doses) of study drug prior to the initial study evaluation (cycle 3 day 1 +/- 7days) will not be evaluable for efficacy but may remain on study pending a discussion with the medical monitors Dr. Modi or Dr. Ramchandren. Efficacy assessments will be performed as outlined in **Appendix 1** and **Section 7.3**. These assessments are to be conducted until disease progression, withdrawal of consent from study participation, or the end of study. For subjects who discontinue study drug before disease progression is documented, disease assessments will continue in the Posttreatment Phase. The determination of disease status for continuation of treatment will be assessed by the investigator based on the results of the efficacy assessments. For all subjects, documentation of disease progression must be sent within 24 hours to the sponsor's medical monitor.

7.3 Evaluations

7.3.1 Radiographic Image Assessments

During the study, disease response will be assessed using whole body FDG-PET scans and CT scans with IV contrast of the neck, chest, abdomen, and pelvis and any other location where disease was present at screening. Subjects who are intolerant of IV CT contrast agents will have CT scans performed with oral contrast. A separate CT scan and PET scan are preferred but, if the only available modality is combined/dual PET/CT scanner, then the CT portion of a PET/CT may be performed in lieu of a dedicated CT; however, the CT scanning must be done with contrast l to ensure that an optimized CT examination is done. Evaluation of other sites of disease by radiological imaging, physical examination, or other procedures as necessary (to be performed throughout the study using the same method of assessment used to assess disease at

baseline), and review of hematology and clinical chemistry results may be performed at the site level, as determined by the investigator. Magnetic resonance imaging 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). For all other sites of disease, MRI studies do not replace the required neck, chest, abdomen, and pelvic CT scans. Brain MRI and lumbar puncture are required, only if clinically indicated.

Radiological assessments will be performed at Screening, (PET and CT w/ contrast) upon completion of cycle 2 (week 8 PET and CT w/ contrast). Thereafter, CT with contrast will be performed every 12 weeks until disease progression, death, or end of study, whichever comes first. Patients who remain on study without progression at 15 mos. may have subsequent imaging performed every 24 weeks. A PET scan will be performed at Screening and after cycle 2 and at CR. PET scans will also be done at the time of maximal tumor reduction (eg, CR or 2 consecutive CT scans showing no further tumor reduction), relapse from CR, and at suspected disease progression if new lesion was detected on CT.

Subjects who discontinue treatment prior to disease progression (for other reasons such as an adverse event) must continue to have regularly scheduled CT scans/efficacy assessments every 12 weeks up to 15 months after the start of study drug. Thereafter, scan will be performed every 24 weeks until disease progression, or death, or the end of the study, whichever occurs first. It is important that instances of progressive disease be reported to the lead investigators at Karmanos Cancer Institute within 24 hours by means of the tumor response form provided at site initiation.

7.3.2. Positron Emission Tomography (PET)

PET using [18F]-fluorodeoxyglucose (FDG) is important for the complete assessment of response and progression in subjects with HL. Whole body FDG-PET scan (skull base to the proximal femur) should be done at Screening, After 2 cycles of therapy (week 8), at the time of maximal tumor reduction (eg, CR or 2 consecutive CT scans showing no further tumor reduction), relapse from CR, and at suspected disease progression if new lesion was detected on CT.

Assessment of PET results is based on published criteria.[14] Visual assessment is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary. A positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff. Other causes of false-positive scans should be ruled out.

Exceptions include mild and diffusely increased FDG uptake at the site of moderate- or large sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen uptake, and diffusely increased bone marrow uptake within weeks after treatment.

7.3.3 Definition of Measurable and Assessable Disease

Eligible subjects must have at least 1 measurable site of disease.[13] Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma. Each measurable site of disease must be greater than 1.5 cm in the short axis regardless of long axis measurement, and clearly measurable in 2 perpendicular dimensions. Measurement must be determined by imaging evaluation. All other sites of disease are considered assessable, but not measurable.

Up to 6 measurable sites of disease, clearly measurable in 2 perpendicular dimensions, will be followed for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease (this includes splenic and extranodal disease). If there are lymph nodes or lymph node masses in the mediastinum or retroperitoneum larger than 1.5 cm in 2 perpendicular dimensions, at least 1 lymph node mass from each region should always be included. In addition, selection of measurable lesions should be from as disparate regions of the body as possible and PET avid.

All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures as necessary, but is not measurable as defined above. Examples of assessable disease include bone lesions; mucosal lesions in the GI tract; effusions; pleural, peritoneal, or bowel wall thickening; disease limited to bone marrow; and groups of lymph nodes that are not measurable but are thought to represent lymphoma. In addition, if more than 6 sites of disease are measurable, these other sites of measurable disease may be included as assessable disease.

7.3.4. Bone Marrow Assessment

Bone marrow aspirate and biopsy are optional at screening and based on investigator's clinical judgment. However, if there is evidence of marrow involvement at screening, a repeat bone marrow evaluation must be performed at the time of CR to confirm remission. This must be done within 30 days of initial documentation of CR.

7.3.5 Criteria for Response Categories

The response categories being used to assess efficacy are based on the Revised Response Criteria for Malignant Lymphoma.[13] **(See Appendix 4)**

Complete Response

For CR determination, all the following criteria must be met:

1. Complete disappearance of all detectable evidence of disease and disease-related symptoms.
2. All lymph nodes and nodal masses must have regressed on CT to normal size (equal to or smaller than 1.5 cm in the greatest transverse diameter [GTD] for nodes greater than 1.5 cm before therapy, regardless of the short axis). Previously involved nodes that were between 1.1 cm and 1.5 cm in the long axis and more than 1.1 cm in the short axis before treatment must have decreased to or be equal to 1 cm in the short

axis after treatment. All splenic and hepatic nodules and other extranodal disease must have disappeared.
3. PET scan must be negative (for the combined CT+PET assessment of CR). A posttreatment residual mass of any size is permitted as long as it is PET-negative.
4. The spleen and/or liver, if enlarged before therapy on the basis of physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies.
5. If bone marrow was involved before treatment, the infiltrate must have cleared on repeated bone marrow biopsy. If a sample is intermediate by morphology, it should be negative by IHC (if bone marrow was involved before therapy and a radiological CR was achieved, but with no bone marrow assessment after treatment, the response should be classified as a PR.)
6. No new sites of disease are detected during assessment.

Partial Response

For PR determination, all the following criteria must be met:

1. 1. A ≥ 50% decrease in the sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses.
2. No increase should be observed in the size of other nodes, liver, or spleen, meeting the criteria for progressive disease.
3. Splenic and hepatic nodules must regress by ≥ 50% in the SPD or, for single nodules, in the GTD.
4. With the exception of splenic and hepatic nodules, other organs should not have any measurable disease.
5. Bone marrow assessment is not required for PR determination.
6. No new sites of disease should be observed.
7. At least 1 PET-positive site of disease (required for the CT+PET assessment of PR).

Stable Disease

1. A subject is considered to have stable disease when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease.
2. The PET should be positive at 1 or more previously involved sites of disease, with no new areas of lymphoma involvement on the posttreatment CT or PET (for the combined CT+PET assessment of stable disease).

Progressive Disease or Relapsed Disease

Progressive disease or relapsed disease (after CR) is defined as:

1. Lymph nodes should be considered abnormal if the long axis is ≥ 1.6 cm, regardless of the short axis length. If a lymph node has a long axis from 1.1 cm to 1.5 cm, it should be considered abnormal, only if its short axis is >1.0 cm. Lymph nodes ≤ 1.0 cm x ≤ 1.0 cm will not be considered abnormal for progressive disease/relapsed disease.

2. Appearance of any new nodal lesion ≥ 1.6 cm in GTD or ≥ 1.1 cm in short axis during or after the end of therapy even if other lesions are decreasing in size.
3. Appearance of any new unequivocal extra-nodal lesion measuring > 1.0 cm in GTD, not thought to be benign by the reviewer, even if other lesions are decreasing in size.
4. At least a 50% increase from the nadir in the SPD of any previously involved nodes, or in a single involved node, or in the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1 cm must increase by > 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
5. At least a 50% increase from the nadir in the longest diameter of any single previously identified node more than 1 cm in its short axis. For the combined CT+PET assessment of progressive disease, lesions should be PET-positive or the lesion was PET-positive before therapy unless the lesion was too small to be detected with current PET systems (smaller or equal to 1.5 cm in the long axis by CT). Any previously involved FDG positive site that became negative and subsequently became positive will be considered progressive disease. Increased FDG uptake in a previously unaffected site should only be considered progressive disease after confirmation with other modalities. For fluid collection (ascites, pleural, or pericardial effusions) cytology confirmation for presence of lymphoma is required.

7.4 Sample Collection and Handling

Correlative studies evaluating blood samples for T cell behavior and cytokine expression as well as fluorescence in situ hybridization of tumor samples are required during this study. For blood samples, study kits will be provided with shipping instructions. A detailed description of these instructions are noted in the **Lab Manual**.

For tissue block submission, a representative amount of tissues in a paraffin embedded block should be shipped to the address noted in the **Lab Manual.**

The appropriate personnel at the Karmanos Cancer institute (noted on instructions) should be notified at least 24 hours prior to shipment.

8 SUBJECT COMPLETION AND WITHDRAWAL

8.1 Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost-to-follow up, or has not withdrawn consent before the end of the study.

8.2 Withdrawal from Study Treatment

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

If a subject's study treatment must be discontinued this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment should be discontinued if:

- The subject experiences overt disease progression or relapse
- Unacceptable toxicity
- The subject becomes pregnant
- The subject refuses further treatment with the study drug
- A serious protocol violation has occurred, as determined by the principal investigator

The investigator must notify the medical monitor within 24 hours if a subject has been determined to have disease progression and provide documentation of disease progression. If a subject discontinues study treatment before the onset of disease progression, end of treatment and posttreatment assessments should be obtained and follow-up of scheduled assessments should be continued.

Refer to Section 7.1.1 for instructions regarding the posttreatment efficacy assessments. The reason(s) a patient discontinues treatment will be recorded on the CRF.

8.3 Withdrawal from Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented. When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. A subject who withdraws will not be replaced.

9. STATISTICAL CONSIDERATIONS

9.1. Objectives

The primary objective is estimation of the overall response rate. Secondary objectives are estimation of duration of response and progression free survival. The exploratory objectives are identification of genes of interest, estimation of the T cell subset alteration and estimation of the association of PDL1 and PDL2 overexpression by FISH with overall response.

9.2. Design

This is a multicenter, single arm, single stage phase II study designed to estimate the efficacy of ibrutinib in evaluable patients with relapsed, refractory Hodgkin's lymphoma. A participant will be deemed response evaluable if he/she has completed at least one cycle of therapy, has at least one imaging study (CT, MRI or PET) and has not missed >25% of treatment dose (14 doses) prior to cycle 3 day 1. Any participant receiving at least 1 dose of ibrutinib will be considered evaluable for toxicity analysis.

9.3. Endpoints

9.3.1. Primary Endpoints

- **Overall Response Rate (ORR)**

Overall response rate (ORR) is defined as the proportion of participants having a complete (CR) and partial (PR) response.

9.3.2. Secondary Endpoints

- **Duration of response (DOR)**

Duration of response is measured from date of documented tumor response, CR or PR, to date of disease progression.

- **Progression Free Survival (PFS)**

Progression-free survival is measured from date of study entry to date of progression or death, whichever occurs first.

9.3.3. Exploratory Endpoints

The influence of ibrutinib on T cell behavior and antitumor effect will be assessed using pre-therapy and post therapy flow cytometry measures of Th1 and Th2 at predetermined time points in therapy.

PDL1 and PDL2 copy number analysis on paraffin-embedded tissue sections will be assessed by FISH.

All patients undergoing any exploratory evaluations will be assessed for correlative analysis.

9.4.0 Statistical Analysis Plan

9.4.1. Efficacy Analysis

A one-sample binomial test will be used to assess ORR. The null hypothesis that the ORR is less than or equal to 30% will be rejected if 13 or more participants have an ORR. The ORR will be

reported as a proportion with a 95% confidence interval. DOR and PFS will be reported as medians with 95% confidence intervals using Kaplan-Meier methods to account for censoring.

9.4.2. Safety Analysis

Frequency of grade 3 or higher adverse events will be tabulated as will all grade 1 and 2 adverse events with frequency greater than 5%, e.g. occurring in 2 or more individuals.

9.4.3. Biomarker Analyses

- Pre/Post Th1 Th2 Changes for ORR+ and ORR- individuals

McNemar's test will be used to evaluate the statistical significance of pre /post therapy changes in Th1 and Th2 positivity separately for those who have an ORR and for those who do not. A conditional logistic regression model will be used to explore whether pre-post changes in Th1 and Th2 are predictive of ORR.

- Association of PDL1 and PDL2 positivity with ORR

The association between PDL1 and PDL2 positivity will be explored using Fisher's exact test. A logistic regression model will be used to explore the association of PDL1 and PDL2 copy gain with ORR.

9.5. Sample Size Determination

A study of 31 evaluable participants was deemed feasible. To accomplish this with an expected dropout not evaluable rate of 12%, a total sample population of 35 patients will be consented. We specified statistical power of 85% to distinguish a null hypothesis value of 30% against an alternative value of 50% assuming a binomial test of one proportion with a target, one-sided type error of 11%. Under these assumptions the null hypothesis will be rejected if there are 13 or more ORRs among the 31 participants.

9.6 Accrual Rate, Accrual Duration and Expected Study Duration

The expected accrual rate across the 4 institutions is 35 participants per year. Thus it is expected that the duration of accrual will be one year. An additional year is planned for evaluation of the primary, secondary and safety endpoints.

10. ADVERSE EVENT REPORTING

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

10.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject 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.

The term “disease progression” should not be reported as an adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

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

The following are NOT considered AEs:

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

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

- ***Asymptomatic Treatment Related Lymphocytosis:*** *This event should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.*

10.1.2 Serious Adverse Events

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

- Results in death (i.e., the AE actually causes or leads to death).

- Is life-threatening. Life-threatening is defined as an AE in which the subject 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 IND 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 (i.e., the AE results in substantial disruption of the subject'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 subject or subject 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.

10.1.3 Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v m 4.03) will be used for grading the severity (intensity) of *nonhematologic* AEs. The CTCAE v 4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v m4.03, 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 subject's daily activities

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, 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 subject's usual daily activity, and require systemic drug therapy or other treatment

- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death

- Grade 5 (Death related to AE) – experiences which result in subject death

10.1.4 Causality (Attribution)

The Investigator is to assess the causal relation (i.e., 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.

10.2 Unexpected Adverse Events

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

anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

10.3 Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

10.3.1 Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation time points during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

If an adverse event is identified by the physician or staff during a non-evaluation time point the AE should also be recorded and reported in the manner by which all other AEs are processed.

10.3.2 Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from ingestion of study drug until 30 days following the last dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported. All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

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.

If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

10.3.3 Pregnancy

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

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

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

10.3.4 Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

10.3.6 Adverse Events of Special Interest (AESI)

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

10.3.6.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

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

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

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 10.3.6 above.

10.3.7 Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A).

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MEDWATCH. A final report to document resolution of the SAE is required. The Pharmacyclics protocol number Ibrutinib PCI-32765 should be included on SAE reports to Pharmacyclics. A copy of the fax transmission confirmation of the SAE report to Pharmacyclics should be attached to the SAE and retained with the patient records. The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

SAEs and AESIs must be reported within 24 hours of awareness of the event. Each site is responsible for reporting these events to both Pharmacyclics and KCI via email or fax:

Pharmacyclics:

AEintakeCT@pcyc.com

Fax: 408-215-3500

Karmanos:

houdec@karmanos.org

Fax: 313-576-8368

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

- The event resolves
- The event stabilizes

- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

10.4 Reporting to Regulatory Agencies:

Serious adverse events that are unlisted/unexpected, at least possibly associated to the study drug, and that have not previously been reported in the Investigators brochure, or reference safety information document will be forwarded to FDA by the IND holder (Karmanos) according to 21 CFR 312.32.

It is the responsibility of the Investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

11 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12 DATA AND SAFETY MONITORING

1. Scheduled investigator meetings will be held monthly or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and research staff involved with the conduct of the protocol.

2. During these meetings the investigators will discuss:

    - Safety of protocol participants (adverse events and reporting)
    - Validity and integrity of the data (data completeness on case report forms and complete source documentation)
    - Enrollment rate relative to expectation of target accrual, (eligible and ineligible participants)
    - Retention of participants, adherence to the protocol and protocol deviations
    - Protocol amendments

3. In addition, Data and Safety Monitoring Reports (DSMR) of the research meetings will be completed by the Study Coordinator from each site and submitted to the Karmanos Data and Safety Monitoring Committee (DMSC) monthly for review. **(See Appendix 5)** The DSMC will review safety of study subjects and will recommend continuation or closure of

the study. The DSMC will review the safety data quarterly and will recommend termination if they judge the rate and severity of AEs to be unacceptable. The DSMC's recommendations will guide study conduct.

4. The Barbara Ann Karmanos Cancer Institute, Data and Safety Monitoring Committee (DSMC) is composed of medical providers, pharmacists and research staff and provides the primary oversight of data and safety monitoring for KCI Investigator-initiated trials.

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

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

12.2 Informed Consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation of the informed consent process will be documented in the patient's records. The original consent form must be maintained in the Investigator's study files.

12.3 Protected Subject Health Information Authorization

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with

applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Study personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection.

Exploratory biomarker and pharmacokinetic research is not conducted under standards appropriate for the return of data to subjects. In addition, the researchers cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

12.4 Study Files and Record Retention

Investigational Study Drug Accountability for the drug is the responsibility of the local principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol and Good Clinical Practice. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and disposal of the drug (if applicable and if approved by KCI) will be maintained by the clinical site.

Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers. Please refer to Section 5.4.1.3 for additional details.

All research study documents will be retained in accordance with E6 Good Clinical Practice: Consolidated Guidance as stated "Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor." It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Iron Mountain (IM) storage facility provides long-term storage of research documents for Karmanos Cancer Institute, Clinical Trial Office.

12.5 Study Monitoring/Audit Requirements

Clinical trial data will be captured in OnCore's (Clinical Trial Management System) electronic data capture system. Site personnel will be trained on the eCRF system by the Karmanos OnCore administrator. Trial data entered in Oncore will be verified by source documentation.

CRFs should be completed by within 10 business days of the availability of clinical documentation of a study visit. Data clarification and queries should be completed within 7 working days of notification.

Each participating site will submit source documents to KCI's clinical trials office. A KCI CTO monitor specialist will remotely monitor essential clinical trial data. Frequency of monitoring will be based on accrual at a site but will occur at least once every 1 month if a patient has been enrolled.

Monthly screening and enrollment logs are to be sent to the KCI Lead Study Coordinator.
If deemed necessary by the primary site or sponsor an audit team may review contracted site data and materials in an on-site review.

12.6 Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements. Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical study data are credible.

12.7 Protocol Amendments

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

12.8 Publication of Study Results

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

12.9 Study Discontinuation

Per the IST Contract, the Investigator reserves the right to terminate the study at any time. Should this be necessary, the Investigator will arrange discontinuation procedures in partnership with Pharmacyclics. In terminating the study, the Investigator will assure that adequate consideration is given to the protection of the subjects' interests. Pharmacyclics may terminate

the study for reasons including, but not limited to: evidence that the PI or an involved investigator is unqualified to conduct research or fulfill sponsor responsibilities (e.g., is listed on a debarment or ineligible investigator list); failure to meet timelines or achieve agreed upon milestones; a known or perceived risk to patient well-being is identified; or breach of contract. Additional grounds for termination are outlined in the IST Agreement.

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14 APPENDICES

Appendix 1. Schedule of Assessments

Study Visits	Screening Phase	Treatment Phase (1 cycle = 28 days)								Suspected PD	Complete Remission	End-of-Treatment	Pre-PD FU
		Cycle 1			Cycle 2		Cycles 3 –7	Cycles 8–14	Cycles 15 – Term				
		D1 (baseline)	D2	D15	D1	D15	D1	D1	D1	Any time		Within 30 D after treatment d/c	q 12 weeks.
Study Visit Windows	-28 days	± 3 days beginning cycle 2 day 1								Any time		+ 3 days	± 7 days
Procedures													
Informed consent	x												
Medical history	x	x			x		x	x	x[j]	x		x	
Confirm eligibility [k]	x	x											
Tumor Biopsy	x[f]									x[f]			
Concomitant medications	x	x		x	x	x	x	x	x[j]			x	
Adverse events [a]		x		x	x	x	x	x	x[j]			x	
Study drug compliance review		x			x		x	x	x[j]			x	
Height	x												
Physical exam, vital signs, weight, ECOG	x	x		x	x	x	x	x	x[j]	x		x	x
Disease assessment:													
PET/CT scan[g]	x						x[g]	x[g]	x[g]	x	x	x	
CT/MRI scan[i]	x[i]						x[i]	x[i]	x[i]	x[i]	x[i]		x[i]
Bone marrow biopsy/aspirate [r]	x										x		
Disease-related symptoms[s]	x	x			x		x	x	x[j]	x		x	x
Overall response assessment							x[g,i]	x[i,g]	X[i]	x			x
Hematology [b]	x	x		x	x	x	x	x	x[j]			x	x
Serum chemistry [c]	x	x		x	x	x	x	x	x[j]			x	x
Serum Pregnancy Test	x												
Creatinine clearance (Cockcroft-Gault)	x												
Biomarker serum samples		x[e]	x[e]	x[e]	x[e]					x[e]			
Hepatitis serologies [d]	x												
Coagulation panel [h]	x												
12-lead ECG [x]	x				If clinically indicated (e.g., subjects with palpitations, lightheadedness)								
Any new anticancer therapy													x
Ibrutinib 560mg daily x 28 days dispensed [p]		x			x		x	x	x[j]				

D = day; Term = treatment termination; d/c = discontinuation; PD = progressive disease; FU = follow-up;

[a] AEs are reported from the time the patient ingests study drug until 30 days following last dose of study drug. In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as adverse events for the duration of the study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

[b] Hematology includes: complete white blood count with differential, hemoglobin, hematocrit, platelet count.

[c] Serum chemistry includes sodium, potassium, calcium, albumin, glucose, creatinine, AST, ALT, alkaline phosphatase, LDH, total bilirubin, and Uric Acid.

[d] Hepatitis B serologies include Hepatitis B IGG antibody, antigen and core antibody . If core antibody is positive the patient will need negative PCR to be eligible for study. Hepatitis C serologies include Hepatitis C IGG antibody.

[e] Serial serum samples pre and post therapy will be assessed for Th1 ((IFN-g) and Th2 cytokines (IL-10, IL-4 and IL-13) at 4 distinct time points (pre-dose cycle 1 day one, cycle 1 day 2 , cycle 1 day 15) , cycle 2 day 1 and at the time of progressive disease. All samples must be PRE-DOSE on date of draw. Utilize provided kits labeled per directions. Refer to Lab manual

[f] Fresh tumor biopsy is highly recommended. The biopsy should be a lymph node excision whenever possible. If lymph node excision is not possible then core needle biopsies (minimum of 4 cores) are required. If fresh tumor tissue is unobtainable, a formalin-fixed paraffin embedded (FFPE) tumor block must be sent to the laboratory for correlative analysis.

[g] PET/CT performed during screening, cycle 3 D1 (window of + or – 7 days) then at maximal tumor reduction on consecutive CT scans w/ contrast or at CR.

[h] Coagulation panel includes PT, aPTT and INR

[i] CT performed with contrast during screening, cycle 3 day 1 (+/- 7 day window) then every 12 weeks (+/- 7 days window) until cycle 15. Thereafter CT with contrast performed every 24 weeks (+/- 7 days)

[j] Every odd cycle (Cycles 15, 17, 19, 21, 23, 25)

[k] It is required that patients continue to meet eligibility on Day 1 of cycle 1 prior to dosing with the exception of the coagulation panel. If the subject met eligibility criteria for the coagulation panel during screening, it does not need to be repeated to re-confirm eligibility on C1D1.

[p] Day 1 and 15 of C1 and C2 will be administered at the investigational site. Subsequently, day 1 of each cycle are taken on site until cycle 15. Beyond cycle 15 drug dispensation and clinic visits occur only on odd numbered cycles.

[r] Bone marrow biopsy and/or aspirate is optional per investigator's decision at screening however if positive must be performed at CR

[s] Disease-related symptoms include weight loss, fatigue, fever, night sweats, pruitis abdominal pain/discomfort due to splenomegaly including early satiety, and anorexia.

[x] ECG's Must be performed at screening. ECG may be repeated at the investigator's discretion (e.g., palpitations, lightheadedness or new onset dyspnea).

Appendix 2. ECOG Status Scores and Formulas

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
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, e.g., light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

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Cockcroft-Gault Equation

(140-Age) * Mass (in kg)] \ [72 * Serum creatinine (in mg/dL)]

*If the patient is female, multiply the above by 0.85

Appendix 3. Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx . The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

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

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

Appendix 4. Response Criteria

Revised response criteria for lymphoma

Response criteria	PET-CT-based response	CT-based response
Complete remission (CR)		
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5-PS**	Target nodes/nodal masses must regress to ≤1.5 cm in LDi
	No extralymphatic sites of disease	
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial remission (PR)		
Lymph nodes and extralymphatic sites	Score 4 or 5** with reduced uptake compared with baseline and residual mass(es) of any size	≥50% decrease in SPD of up to 6 target measureable nodes and extranodal sites
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy, or an interval scan	Not applicable
No response or stable disease (SD)		
Target nodes/nodal masses, extranodal lesions	No response: score 4 or 5 with no significant change in FDG uptake from baseline, at interim or end of treatment	Stable disease: <50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Progressive disease (PD)

Individual target nodes/nodal masses, extranodal lesions	Score 4, 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	An individual node must be abnormal with: • LDi >1.5 cm • Increase by ≥50% from PPD nadir An increase in LDi or SDi from nadir • 0.5 cm for lesions ≤2 cm • 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
New or clear progression of pre-existing non-measured lesions	New FDG-avid foci consistent with lymphoma rather than another etiology, e.g. infection, inflammation. If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	New or recurrent splenomegaly New lesions Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis if less than 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG avid foci	New or recurrent involvement

Deauville Criteria for PET Score

1 no uptake
2* uptake <mediastinum
3* uptake >mediastinum but <liver
4 Uptake moderately increased compared to the liver at any site.
5 Uptake markedly increased compared to the liver at any site or/and new sites of disease.

* If mediastinal blood pool activity is equal or greater than liver then the uptake within the lesion should be compared with liver (lesion uptake less than liver=score 2; lesion uptake equal to liver=score 3).

Source: Report on the Second International Workshop on interim positron emission tomography in lymphoma held in Menton, France, 8-9 April 2010. Meignan M, Gallamini A, Haioun C, Polliack A. Leuk Lymphoma 51; 2010:2171-80.(33) Cheson et al. JClin Oncol 32 2014

Appendix 5

Barbara Ann Karmanos Cancer Institute

Data and Safety Monitoring (DSM) Report

PROTOCOL #: _____ **REPORT DATE:** _____

PROTOCOL TITLE		
ATTENDANCE		

PROTOCOL ACTIVITY SINCE LAST REPORT			
Accrual Goal:	Eligible:		Total number of AE's to date:
Accrual to Date:	Ineligible (provide reason):		
Accrual Since Last Monthly Report:			

SPECIFICALLY FOR PHASE I TRIAL &/OR DOSE ESCALATING TRIALS:	
DOSE LEVEL	ACCRUAL
1	
2	
3	

RECORD ALL GRADE 3, 4, AND 5 AE'S AND GROUP BY CTCAE CATEGORIES. RECORD THE DATE OF THE OCCURRENCE, ATTRIBUTION AND IF REPORTABLE TO THE IRB. SHADE THE ROWS OF THE AE'S THAT HAVE OCCURRED FOR THIS REPORT. ATTACH THE IRB REPORT FORM FOR THE REPORTABLE EVENTS THAT OCCURRED ON THIS REPORT.

Pt. ID#	Category and type of adverse reaction	Date of Occurrence	Grade[1]	Attribution[2]	Reportable to IRB (Y/N) Yes with date

1. Grade: 1-Mild, 2-Moderate, 3- Severe, 4-Life-threatening, or 5- Death.
2. Attribution: 1-unrelated, 2 - unlikely, 3 - possibly, 4 - probably, or 5 - definitely

OFF TREATMENT □ Provide reason [progression, death, toxicity, completed therapy, etc.].			
PROTOCOL DEVIATIONS □ Accidental or unintentional change from the protocol.			
PROTOCOL AMENDMENTS □ Include date submitted and approved by the IRB.			
OTHER COMMENTS			
Investigator Signature/Date:		**Study Coordinator Signature/Date:**	

Appendix 6

See attached diary

Appendix 7. Child-Pugh Score

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

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

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, Pietroni MC, Williams R . "Transection of te oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 1973;60: 646-9.