Targeting BTK with Ibrutinib after Autologous Stem Cell Transplantation in "Double-Hit" B-Cell Lymphoma

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1.0 Objectives

1.1 Primary objective

1.1.1 Determine the efficacy of the use of Ibrutinib maintenance after autologous stem cell transplantation (SCT) in double-hit lymphoma, defined by the 2-year disease-free survival (DFS) rate.

1.2 Secondary objectives

1.2.1 Estimate safety and toxicity, DFS, and overall survival (OS).

1.2.2 Estimate efficacy and DFS at 3, 6, 9, 12 months and every 6 months thereafter for 3 years.

1.3 Tertiary objectives

1.3.1 Exploratory Correlative studies.

2.0 Background

2.1 Oncogenes involved in DHL

Double-hit lymphoma (DHL) has been defined as a B-cell lymphoma with MYC/8q24 rearrangement in combination with a translocation involving another gene, such as BCL2, BCL3 or BCL6.[1-3] The most common form of DHL has translocations involving MYC and BCL2, also known as MYC/BCL2 DHL. BCL2, located at 18q21, encodes an anti-apoptotic protein. The t(14;18)(q32;q21) juxtaposes BCL2 with the IGH gene enhancer at 14q32, resulting in BCL2 overexpression. BCL2 also has a role in physiological DNA repair. It is hypothesized that the coexistence of MYC and BCL2 translocations in MYC/BCL2 DHL results in markedly increased cell proliferation and decreased apoptosis, resulting in rapid tumor growth.

2.2 Morphology and Immunophenotyping

MYC/BCL2 DHL was once thought to be uncommon, representing, 1% of all lymphomas and approximately 4% of high-grade B-cell lymphomas reported in the older literature.[1,-6] More recent studies in which MYC and BCL2 were tested routinely, however, have shown that MYC/BCL2 DHL is more common than had been appreciated with a frequency that is approximately 10%.[7] The historical underestimation of its frequency was likely due to at least 2 reasons. The first is that traditionally cases of aggressive e B-cell lymphoma have not been routinely tested by conventional cytogenetics or FISH. Secondly, translocations can be difficult to recognize using conventional karyotyping methods in a subset of tumors.[8]

Approximately 80% to 85% of cases of MYC/BCL2 DHL arise in patients de novo, whereas 15% to 20% of cases are thought to have progressed from follicular lymphoma. Most cases of MYC/BCL2 DHL morphologically resemble diffuse large b-cell lymphoma (DLBCL) or B cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU).[1-3] Translocations can be difficult to recognize using conventional karyotyping methods in a subset of tumors. Traditionally, cases of aggressive B-cell lymphoma have not been routinely tested by conventional cytogenetic or fluorescence in situ hybridization (FISH). Pedersen et al[7] studied 157 patients with DLBCL or BCLU. All 157 cases were analyzed by using FISH with MYC and BCL2 break-apart probes and 11% of the cohort was MYC/BCL2 DHL. This subset represented 7% of de novo lymphomas and 21% of transformed lymphomas. These tumors are of B-cell lineage and have a germinal center B-cell immunophenotype (CD10, BCL6, MUM1/IRF4) with a high proliferation rate.

2.3 Clinical Features

In recent years, a number of small series of MYC/BCL2 DHL have been published.[1-3] DHL occurs mainly in older patients and slightly more often in men. The median age at diagnosis has ranged from 51 to 65 years, which is older than patients with BL (fourth decade), but slightly younger than patients with DLBCL (seventh decade). In another study of 97 children with aggressive B-cell lymphomas, no cases of MYC/BCL2 DHL were identified.[9] Patients with double hit lymphoma have extremely poor adverse prognostic features. Most patients with MYC/BCL2 DHL present with advanced stage disease (Ann Arbor III/IV). Extranodal sites of involvement are frequent, with the bone marrow and central nervous system being involved most commonly. Virtually any extranodal site can be involved. An elevated serum lactate dehydrogenase level is very common in patients with MYC/BCL2 DHL. Most patients have a high-intermediate or high International Prognostic Index (IPI). Snuderl et al[10] compared MYC/BCL2 DHL patients with IPI-matched DLBCL patients and found that the former group had a higher median LDH level at presentation (727 vs. 366 U/L) and higher frequency of bone marrow involvement (59% vs. 23%).

No standardized treatment approach is established. As shown in Table 1, patients with MYC/BCL2 DHL have been treated with different regimens, including traditional chemotherapy regimens and more aggressive chemotherapy. The median overall survival of newly diagnosed MYC/BCL2 DHL patients is very poor, ranging from 2 months to 1.5 years, regardless of the therapeutic regimen employed regimens with or without stem cell transplant. The most common traditional regimens that have been used are R-CHOP (rituximab, cyclophosphamide, daunorubicin, vincristine, prednisone) or CHOP. More aggressive chemotherapy regimens used include Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), R-Hyper-CVAD, and R-EPOCH (Table 1).

Table 1

Study	No. of DH/total Study size (%)	Treatment regimen*	Overall response rate, n/N(%)†	Median Survival, y
Bertrand et al40 2007	10/17 (59)	NA	5/10‡ (50)	< 1§
Johnson et al15 2009	54/54 (100)	RCHOP (11/54);HDC+/- SCTI (6/54); CHOP (23/54); P (14/54)	NA	HD, 0.26; RCHOP, 1.40; CHOP-like, 0.42; P 0.07
Kanungo et al13 2006	14/14 (100)	CT-NOS (11); R¶ (1); CT and BMT (1); CT, BMT, and RT (1)	NA	< 1§
Le Gouill et al10 2007	16/16 (100)	CEEP/COPADM + Auto-SCT/BEAM (1); CHOP/IVAM (1); COPADM/CYVE (3); COPADM (1); COPADM + Auto-SCT/BEAM (1); COPADM + Allo-SCT/Bu/Cy (1) CEEP/DHAP + Auto-SCT/BEAM (1); RCHOP (4); CHOP (1); Steroids# (1); R-CEEP Allo-SCT/TBI/Cy (1)	12/16 (75)	0.42
Macpherson et al112 1999	15/39 (38)	CHOP-variant or cyclophosphamide + MTX (6); HDC +/- SCT (3); P (4)	NA	0.21
Niitsu et al12 2009	19/19 (100)	CyclOBEAP (6); CHOP + HD MTX (3); CHOP (4); RCHOP (3), CyclOBEAP + R (3)	17/19 (89)	1.50
Snuderl et al14 2010	20/20 (100)	R-ICE + MTX/ASCT (1); CHOP (1); RCHOP (3); RCHOP + MTX (6); RCHOP + MTX + ASCT (1); R-EPOCH + MTX (3); CODOX- + MTX/R-IVAC (3); P (1); NK(1)	10/20** (50)	0.38
Tomita et al11 2009	27/27 (100)	CHOP or CODOX-M/IVAC or HyperCVAD (+ R, n = 14; -R, n = 8)††	6/23 (26)††	

(Adopted from Aukema et al. Blood 2001;117:2319-2331).

2.4 Rationale for Stem Cell Transplantation (SCT)

In a recent multicenter respective analysis,[11] newly diagnosed DHL patients were treated with either R-CHOP, or one of the following intensified regimens: R-HyperCVAD, R-EPOCH, R-CODOX-M/IVAC, R-ICE. One hundred six patients were analyzed. Fourteen (13%) were consolidated with SCT (n=1 allogeneic and n=13 autologous SCT). While the induction regimen did not impact survival rates in patients not receiving SCT, SCT in first remission was associated with improved overall survival (*P* = 0.02), and progression-free survival (*P* = 0.006) compared with induction alone.

2.5 Targeting B-cell receptor

The B-cell receptor (BCR) is essential for normal B-cell development and maturation. In an increasing number of B-cell malignancies, BCR signaling is implicated as a pivotal pathway in tumorigenesis.[12,13]

Mechanisms of BCR activation are quite diverse and range from chronic antigenic drive by microbial or viral antigens to autostimulation of B-cells by self-antigens to activating mutations in intracellular components of the BCR pathway. Chronic lymphocytic leukemia (CLL) has been recognized for decades as a malignancy of auto-reactive B-cells and its clinical course is in part determined by the differential response of the malignant cells to BCR activation. Initial antigen selection during transformation or continued antigenic drive appears to play a role in additional B-cell malignancies, including mantle cell lymphoma (MCL) and follicular lymphoma (FL), resulting in activation of the NF- kB pathway.[12,13]

The mechanism of signaling in DHL has not been studied. The hallmark of BL is a translocation of MYC to the Ig heavy chain locus. However, MYC has strong pro-apoptotic effects and requires activation of pro-survival signaling through the PI3K pathway. Because of the MYC/BCL2 translocation in DHL, it is plausible that activation of BCR signaling occurs through a combination of extrinsic signaling, by antigenic drive (as in FL with BCL2), and intrinsic

signaling, due to acquired mutations (as in BL).[12,13] A prominent example of this process is observed in a subset of activated B-cell (ABC) DLBCLs.

Targeted therapy through inhibition of BCR signaling is emerging as a new treatment paradigm for many B-cell malignancies. Bruton's tyrosine kinase (BTK), an essential component of B-cell–receptor signaling, mediates interactions with the tumor microenvironment. In the first clinical trial (see Appendix C., Package Insert) reported with BTK-inhibitor ibrutinib at 560 mg po/day, an overall response of 54% across different B-cell malignancies was reported, 7/9 for MCL,11/16 for CLL, 6/16 for FL (later updated with response in 11/16 patients), and 2/7 for DLBCL.[14] Another study for DLBCL patients showed responses for ABC but not GCB subtypes in agreement with the preclinical data on the importance of BTK signaling preferentially in ABC DLBCL (two partial responses (PR) and one CR out of 10 patients). More recently, overall response rate (ORR) of 71% for treatment naïve CLL patients, 67% for relapsed or refractory patients, and 50% for high risk patients has been reported.[15] A recent report from a phase II study in relapsed MCL (n = 111, 48 previously bortezomib treated) showed ORR of 68% and CR of 21%; after a median of 15.3 months follow up the estimated progression-free survival was 13.9 months.[16]

2.6 Rationale for maintenance ibrutinib after stem cell transplantation in DHL

Despite considerable heterogeneity in biology and clinical course, many mature B-cell malignancies are highly sensitive to kinase inhibitors that disrupt BCR signaling. Relapse remains the major cause of failure after hematopoietic transplantation. Maintenance targeted therapy has been emerging as an important strategy to treat microscopic resistant clones. The safety profile of BTK-inhibitor ibrutinib is encouraging. Specifically, grade 3 or higher hematologic events were infrequent suggesting that extended treatment of the drug may be well tolerated after stem cell transplantation.

2.7 Correlative studies

Various mechanisms of clinical non-responses have been found to Ibrutinib therapy.[13,18] Mutations within the CD79A, CD79 B part of the BCR that increase the response to antigenic drive and activating mutations (CARD11, caspase recruitment domain-containing protein 11) in downstream signal transduction components may confer antigen independent pro-survival signaling. Blood levels of BCR-driven chemokines CCL 3 and CCL 4 (T-cell-recruiting chemokines) are biomarkers of initial response in CLL. MYD88 (myeloid differentiation primary response protein 88) mutations has been shown to induce resistance to ibrutinib in ABC-DLBCL. Recent studies in MCL found that mutations in TRAF2 or BIRC3 are associated with insensitivity to BCR inhibitors.[17] We propose to study these pathways in our study.

Micro-RNAs (miRNAs) are central regulators of gene expression, and their relevance in cancer is now well established.[19] It has been shown recently that MYC plays a key role in determining the miRNA expression signature of DLBCL by negatively regulating the expression of a host of miRNAs and to transcriptionally activate the miR-17-92 cluster.[20] Studying mirRNA in DHL and the impact of ibrutinib on its expression is a correlative study of interest in this study.

2.8 Ibrutinib

2.8.1 Background

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream 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 patients with CLL (at a dose of 420 mg po daily), patients with CLL 17p deletion, MCL (at a dose of 560 mg po daily) who have received at least one prior therapy, and Waldenstrom's Macroglobulemia (WM). 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 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.[21]

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.[22] 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.[23]

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 postdose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

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

2.8.2 Summary of Nonclinical Data

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

2.8.3 Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk.[24] In vitro, ibrutinib is a potent inhibitor of Btk activity (IC50 = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC50 = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression.[25]

Ibrutinib arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models (Herman 2011) Ibrutinib also inhibited adhesion and migration of mantle cell lymphoma (MCL) cells in co-culture and reduced tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression[26]

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

2.8.4 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 560 mg daily, respectively.

2.8.5 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.

2.8.6 Summary of Clinical Data

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

2.8.7 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.

2.8.8 Ibrutinib safety profile

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

For monotherapy studies:

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

For more detailed information refer to the current version of the Investigator's Brochure.

2.8.8.1 **Treatment Discontinuations**

As of 6 April 2013, 71/636 subjects discontinued treatment due to an adverse event, across the monotherapy and combination therapy ibrutinib studies (excluding Study PCYC-1103-CA); 62 subjects receiving monotherapy population and 9 subjects receiving combination therapy. The most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), and cardiac arrest and Richter's Syndrome (3 subjects each).

2.8.8.2 **Bleeding-related events**

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures.

Lymphocytosis and Leukostasis

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk. For subject and ibrutinib management guidance, refer to Section 4.0.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥ 50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/ small lymphocytic lymphoma

(SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

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

Infections
Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE v4). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

Cytopenias
Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

Atrial Fibrillation
Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 6.2.4).

Second Primary Malignancies
Second primary malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Second primary malignancies including non-skin carcinomas have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer.

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

Diarrhea
Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 4.0).

Rash
Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity.

Interstitial lung disease
Cases of interstitial lung disease (ILD) have been reported in subjects treated wih ibrutinib. Randomized, controlled Phase 3 studies did not show an increased incidence rate of ILD in subjects treated with ibrutinib as compared to subjects treated with active control. Subjects should be monitored and evaluated for symptoms (e.g., dyspnea, cough or pyrexia) and treated symptomatically, including interruption of the suspected agent as appropriate.

For subject and ibrutinib management guidance, refer to Section 4.0.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Patients with newly diagnosed double hit in first complete remission, anytime during the first 3 months after chemoimmunotherapy followed by autologous stem cell transplantation if there was no evidence of progression.

3.1.2 Double hit lymphoma is defined as B-cell lymphoma with genetic abnormalities involving A) and in addition, B) and/or C):

A) C-MYC arrangement or amplification by FISH study.
B) BCL2 rearrangement or amplification by FISH study.
C) BCL6 rearrangement or amplification by FISH study.

3.1.3 ANC >/= 1,000, platelets >/= 75,000.

3.1.4 AST and/or ALT < 3 times the ULN.

3.1.5 Creatinine clearance > 30 ml/min (Cockcroft-Gault formula using ideal body weight).

3.1.6 Male or female age >/= 18 years.

3.1.7 ECOG performance status </= 2.

3.1.8 Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.

3.1.9 Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.

3.1.10 Patient should preferably have received a pre-transplant conditioning with rituximab and Carmustine/Etoposide/Cytarabine/Melphalan/Rituxan (BEAM/R) . Other regimens which are similar may be accepted at the discretion of the PI.

3.2 Exclusion Criteria

3.2.1 Prior chemotherapy within 3 weeks, nitrosoureas (carmustine) within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks of first dose of study drug.

3.2.2 Relapsed within three months post-transplant.

3.2.3 History of other malignancies within the past year except for treated basal cell or squamous cell skin cancer or in situ cervical cancer.

3.2.4 Known CNS lymphoma.

3.2.5 Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 (moderate) or 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.

3.2.6 Requires treatment with a strong cytochrome P450 (CYP)3A inhibitor (i.e. Voriconazole, posaconazole, itraconazole, clarithromycin, etc.) or inducer (carbamazepine, rifampin, phenytoin, etc.).

3.2.7 AST and/or ALT >/= 3 times the ULN.

3.2.8 Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or symptomatic ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

3.2.9 Known history of human immunodeficiency virus or active infection with hepatitis C virus or hepatitis B virus or any uncontrolled active systemic infection.

3.2.10 Positive pregnancy test in women of childbearing potential.

3.2.11 Lactating or pregnant or will not agree to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children.

3.2.12 Concomitant use of warfarin or other Vitamin K antagonists.

4.0 Treatment Plan

4.1 Ibrutinib will be started at a daily dose of 560 mg po daily.

4.2 Patients will continue on Ibrutinib until relapse, or AE not managed by dose adjustment, or upon completion of 3 years on ibrutinib. Dose will be adjusted should cytopenia or other non-hematologic toxicity occur (Sections 4.4 and 4.5).

4.3 For patients requiring surgery, ibrutinib should be held 3 to 7 days prior to surgery (depending on surgery type and bleeding risk) and hold for 7 days post-surgery.

4.4 Parameters to hold/interrupt ibrutinib:

- Grade >/= 3 neutropenia with fever.
- Grade 4 neutropenia lasting > 7 days (despite use of GCSF).
- Grade 3 or 4 platelet counts < 50,000/microL in presence of significant bleeding. In subjects with baseline thrombocytopenia, a platelet decrease of 50 to 75% in presence of significant bleeding.
- Grade 4 platelets < 25,000/microL or, in subjects with baseline thrombocytopenia, decrease of > 75% from baseline or < 20,000/microL, whichever is higher.
- Any Grade >/= 3 non-hematologic toxicity.

4.5 Toxicity Management

Toxicity occurrence	Action	Toxicity not related to study drug	Toxicity related to study drug
First	Hold drug until resolution to grade I or to baseline.	Restart at original dose	Restart at 420 mg/day
Second	Hold drug until resolution to grade I or to baseline.	Restart at 420 mg/day	Restart at 280 mg/day
Third	Hold drug until resolution to grade I or to baseline.	Restart at 280 mg/day	Restart at 140 mg/day
Fourth	Hold drug until resolution to grade I or to baseline.	Stop medication, do not re-challenge	Stop medication, do not re-challenge

If the dose of ibrutinib/placebo is reduced, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the Dose Administration eCRF.

Leukocytosis/Leukostasis

A high number of circulating malignant cells (>400000/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 investigator should be contacted.

Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child- Pugh class B or C) are excluded from study participation. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Section 4.5).

5.0 Background Drug Information

5.1 Study Medication

5.1.1 Ibrutinib

5.1.2 Formulation/Packaging/Storage/Disposal

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

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

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

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

Any unused or expired drug will be discarded following the MD Anderson Investigational Pharmacy's standard operating procedures.

5.1.3 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 patients 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.

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

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

5.1.4 Overdose

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

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

Refer to Section 10.0 for further information regarding AE reporting.

5.1.5 Pharmacokinetics

Distribution: ~10,000 L

Bioavailability: Administration with food increased exposure ~2-fold (compared to overnight fasting)

Protein binding: ~97%

Metabolism: Hepatic via CYP3A (major) and CYP2D6 (minor) to active metabolite PCI-45227

Half-life elimination: 4-6 hours

Time to peak: 1-2 hours

Excretion: Feces (80%; ~1% as unchanged drug); urine (<10%, as metabolites)

6.0 Concurrent 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. 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 100 mg per day of prednisone or equivalent are permitted.

After consultation with the investigator the following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

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

As stated above, patients treated on this protocol may require supportive care treatment (concomitant medications). These medications are considered standard of care and have no scientific contribution to the protocol; therefore no data will be captured on various medications needed or their side effects.

6.2 Medications to be Used with Caution

6.2.1 CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

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

- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg (for 840 mg/day dose, reduce to 280 mg) for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Section 5.1.3)

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

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

A list of common CYP3A inhibitors and inducers is provided in Appendix 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 IC50 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.

6.2.4 Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. 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 6.4).

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

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 is 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.

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 patients 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, 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.

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 and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

6.4.3 Emergency Procedures

For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, or for at least 7 days after the urgent surgical procedure, whichever is longer.

7.0 Study Evaluations

7.1 Disease monitoring

7.1.1 Patients will be assessed at 3, 6, 9, and 12 months after the first dose of ibrutinib, then every 6 months for 3 years. After 3 years, patients will be followed according to MD Anderson's Department of Stem Cell Transplant and Cellular Therapy standard of care guidelines.

Table of Evaluations

Protocol 2014-0096	Within 4 weeks of the 1st dose	Weekly for the first 4 weeks after 1st dose	Then every 2 weeks for 4 weeks after 1st dose	Monthly[1]	1 month (+/-5 days) after 1st dose	2 months (+/-5 days) after 1st dose	3 months (+/-5 days) after 1st dose	6 months (+/-15 days) after 1st dose	9 months (+/-15 days) after 1st dose	12 months (+/-15 days) after 1st dose	Every 6 months (+/-15 days) for 3 years after 1st dose[6]	Yearly post-transplant while taking ibrutinib
History and physical exam, vital signs, performance status							X	X	X	X	X	X
CBC, creatinine, liver function tests		X	X	X[1]								
Peripheral blood CD4, CD8, immunodeficiency panel[2]							X	X	X	X	X	X
Immunoglobulin levels							X	X	X	X	X	X
Bone marrow aspiration/biopsy (unilateral)					X[3]		X	X	X	X	X	
CT scans (neck, abdomen, pelvis)							X	X	X	X	X	X
PET[4]												X
Research Tests (Optional)	X[5]				X[5]		X[5]	X[5]				

[1] Monthly after 1st study drug dose, if no need for dose reductions or holding of medication. Labs may be checked more often at physician's discretion.

[2] Only repeat immunodeficiency panel in patients with recurrent infections.

[3] No bone marrow aspiration/biopsy at Month 1 after the 1st dose if negative pre-transplant.

[4] PET only if positive at transplant, and do not repeat after it becomes negative.

[5] See protocol Section 7.4 for details.

[6] After 3 years, patients will be followed according to MD Anderson's Department of Stem Cell Transplant and Cellular Therapy standard of care guidelines.

7.1.2 The International Working Group response criteria will be used.

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	> 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	> 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by >50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, >50% increase in SPD of more than one node, or >50% increase in longest diameter of a previously identified node > 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [18F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

7.2 Safety Monitoring

The following labs may be done at the designated time points by their home physician and the results sent to the MDACC clinical research team. The PI/treating physician will review these labs, determine clinical significance, and sign/date the results. Concomitant medication data will not be collected.

7.2.1 Complete blood counts, creatinine, LFTs as follows:

- Weekly for the first four weeks of therapy, then
- Every 2 weeks for 4 weeks, then
- Monthly thereafter *(If no need for dose reductions or holding of medication)*

7.2.2 Patients may have labs checked more frequently at the discretion of the physician.

7.3 Outside Physician Participation During Treatment

MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician.

This will be documented in the patient record. Protocol-specific treatment decisions must be made by the MDACC physician.

A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix G.).

Protocol required evaluations outside MDACC will be documented by fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.

Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

A copy of the informed consent, protocol abstract, and Table of Assessments (Appendix D.) during treatment will be provided to the local physician.

Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

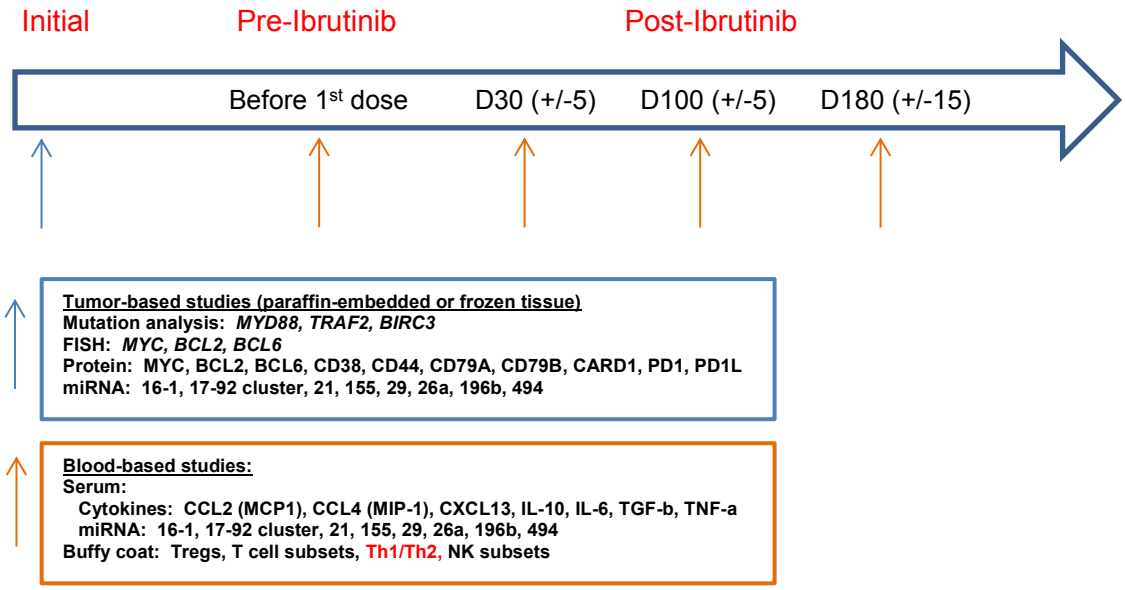
Patients will return to MDACC every 3, 6, 9, and 12 months, then every 6 months for 3 years after the first dose of ibrutinib, then yearly as long as they are receiving ibrutinib.

7.4 Optional lab studies

7.4.1 Rationale

Please see Section 2.7.

7.4.2 Tests and Schedule



8.0 Criteria for Removal from the Study

8.1 Disease progression.

8.2 Intolerable side effects.

8.3 Unable to follow study directions.

8.4 Withdrawal of consent.

8.5 Completion of 3 years on study drug.

9.0 Statistical Considerations

We expect to accrue a total of 30 autologous stem cell transplant patients. The primary endpoint is to estimate the disease-free survival rate at 2 years. With 30 patients, we have 80% power to detect an improvement in this rate from 50% associated with standard of care to 75%, assuming a 5% Type I error rate using an exact test for a single proportion (calculated in nQuery v7.0). The primary endpoint will be estimated using a 95% confidence interval, and drop-outs will be counted as non-responders. A toxicity monitoring rule is provided below to ensure the study will stop early if there is a high chance of a toxicity rate higher than 30%. A futility monitoring rule is not included since it is unlikely that this maintenance therapy will worsen the 2-year disease-free survival rate compared to standard of care, i.e. no maintenance.

The monitoring rule will be assessed by the study team with assistance as necessary from the Department of Biostatistics at MD Anderson Cancer Center.

Toxicity monitoring rule: If at any time there is a high probability of observing more than a 30% toxicity rate, the study will be stopped. Toxicity includes any grade IV toxicity requiring a drug hold of more than 2 weeks within the first four cycles that does not resolve with dose reduction. Bayesian sequential monitoring[29] will be employed to perform interim safety monitoring targeting a toxicity rate of not more than 30%. Patients will be monitored in cohorts of 1. The study will be stopped if

$$\Pr [\text{prob(toxicity)} > 0.30 \mid \text{data}] > 0.97$$

That is, if we determine that there is a greater than 97% chance that the toxicity rate is greater than 30%, the study will be stopped. We assume a beta (0.6, 1.4) prior distribution for the experimental toxicity rate, which has a mean of 0.3 corresponding to the 30% target toxicity rate. We assume a beta (300, 700) prior distribution for the standard treatment toxicity rate. Stopping boundaries corresponding to this probability criterion are to terminate accrual if

Table 2

If there are this many (or more) patients with Toxicity	**Total number of patients evaluated**
Never stop with this many patients	1-3
4	4
5-6	5-6
6-9	7-9
7-11	10-11
8-13	12-13
9-16	14-16
10-18	17-18
11-21	19-21
12-23	22-23
13-26	24-26
14-28	27-28
15-29	29
Always stop at 30 patients	30

Patients must complete at least two months of treatment or have toxicity to be included in the rule. Patients who complete at least two months but drop out without experiencing toxicity will be included but not counted as toxicities.

This stopping rule was chosen to assure that the probability of early stopping would be approximately 7% if the true rate of toxicity was no more than 30%. The operating characteristics of this rule are shown below. The stopping boundaries and operating characteristics were calculated in the Department of Biostatistics using the software Multc Lean Desktop v1.2.0.

Table 3. Operating Characteristics for Toxicity Stopping Rule

If the true toxicity rate is…	Early Stopping Probability	Achieved Sample Size 25th, 50th, 75th percentiles		
0.1	0.0002	30	30	30
0.2	0.0070	30	30	30
0.3	0.0709	30	30	30
0.4	0.3114	21	30	30
0.5	0.6875	9	18	30
0.6	0.9338	6	9	16

Secondary and tertiary objectives

For secondary objectives, we will estimate response, safety, and toxicity at 3, 6, 9, and 12 months after treatment initiation and then every 6 months x 3 years with a 95% confidence interval. We may also estimate specific response types such as humoral and cellular. This data will be used to inform future studies. Kaplan-Meier[30] survival curves will be used to estimate overall survival and progression-free survival. We will also assess the rates of organ toxicity. Cox proportional hazards regression analysis will be used to model the association between overall survival and progression-free survival and disease and demographic covariates of interest, including data from the correlative cytokine, immune, and Mir studies.

10.0 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 Definitions

10.1.1 Adverse Events

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

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

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 patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.
- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with 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. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.*

10.1.2 Severity Criteria (Grade 1-5)

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

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

10.1.3 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 package insert (Appendix C.) 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 package insert referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral

vasculitis would be “unexpected” (by virtue of greater specificity) if the package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the package insert 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.

Adverse events will be documented and entered into the electronic case report form in MD Anderson’s PDMS/CORe systems and in the medical record. All protocol specific data will be entered into PDMS/CORe.

10.3.2 Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the first dose of study drug until 30 days following the last dose of study drug and will be collected in MD Anderson’s Clinical Oncology Research (CORe) system. We will record the AEs’ start date, resolution date, and maximum grade.

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. (See Section 10.1.1)

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 (e.g., 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 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days 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 by completing will need to be reported to Pharmacyclics 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.

10.3.5 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 Pharmacyclics Drug Safety per SAE reporting timelines.

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.

Events meeting the definition of major hemorrhage will be captured as an event of special interest as defined above.

10.3.6 Serious Adverse Events (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

10.3.7 Investigator Communications with Pharmacyclics, Inc.

All serious adverse events will be reported on the MD Anderson SAE Form and will be sent via email (AEintakePM@pcyc.com) or fax ((408) 215-3500) to Pharmacyclics Drug Safety, or designee within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Investigator.

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)

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

11.0 Study Administration and Principal Investigator Obligations

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.

12.0 References

1. Aukema SM, Siebert R, Schuuring E, et al. Double-hit b-cell lymphomas. Blood 2011;117:2319-2331.
2. Friedberg JW. Double-hit diffuse large b-cell lymphoma. J Clin Oncol 2012;30:3439-3443.

3. Li S, Lin P, Young KH, et al. MYC/BCL2 double-hit high-grade b-cell lymphoma. Adv Anat pathol 3013;20:315-326.
4. Pedersen MO, Gang AO, Poulsen TS, et al. Double-hit BCL2/MYC translocations in a consecutive cohort of patients with large B-cell lymphoma — a single centre's experience. Eur J Haematol 2012;89:63-71.
5. Lu B, Zhou C, Yang W, et al. Morphological, immunophenotypic and molecular characterization of mature aggressive B cell lymphomas in Chinese pediatric patients. Leuk Lymphoma. 2011;52:2356–2364.
6. Snuderl M, Kolman OK, Chen YB, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. Am J Surg Pathol. 2010;34:327–340.
7. Ganghi M, Petrich A, Cassaday R, et al. Impact of induction regimen and consolidative stem cell transplantation in patients with double hit lymphoma (DHL): A large multicenter retrospective analysis. *Blood* 2013;122: Abstract 640.
8. Khouri IF, Champlin RE. Nonmyeloablative allogeneic stem cell transplantation for non-hodgkin lymphoma. Cancer J 2012;18:457-462.
9. Fowler N and Davis E. Targeting B-cell receptor signaling: changing the paradigm. Hematology 2103, 553-560.
10. Young RM and Staudt LM. Targeting pathological B cell receptor signalling in lymphoid malignancies. Nature Reviews 2013;12:229-243.
11. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2013;31(1):88-94.
12. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32–42.
13. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013;369:507-516.
14. Rahal R, Frick M, Romero R, et al. pharmacological and genomic profiling identifies NF-κB–targeted treatment strategies for mantle cell lymphoma. Nature Medicine 2014;20:87-92.
15. Allen JL, Tata PV, Fore MS, et al. Increased BCR responsiveness in B cells from patients with chronic GVHD. Blood (on line, Feb 14, 2014).
16. Esquela-Kerscher A, Slack FJ. Oncomirs – microRNAs with a role in cancer. Nat Rev Cancer 2006;6:259-269.
17. Li C, Sang-Woo Kim SW, Rai D, et al. Copy number abnormalities, MYC activity, and the genetic fingerprint of normal B cells mechanistically define the microRNA profile of diffuse large B-cell lymphoma. Blood 2009;113:6681-6690.
18. Thall PF, Simon R, and Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Statistics in Medicine. 1995;14: 357-379.
19. Kaplan EL and Meier P. Non-parametric estimation from incomplete observations. Journal of the American Statistical Association. 1958;53:457-481
20. Gooley TA, Leisenring W, Crowley J, and Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Statistics in Medicine. 1999; 18:695-706.
21. Bishop GA, Haxhinasto SA, Stunz LL, et al. Antigen-specific B-lymphocyte activation. Crit Rev Immunol 2003;23:165-197.
22. Shaffer AL, Rosenwald A, Staudt LM. Lymphoid malignancies: The dark side of B-cell differentiation. Nat Rev Immunol 2002;2:920-932.
23. Satterthwaite AB, Witte ON. The role of Bruton's tyrosine kinase in B cell development and

function: a genetic perspective. Immunol Rev 2000;175:120-127.
24. Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. ChemMedChem 2007;2:58-61.
25. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. Blood. 2011;117:6287-6296.
26. Chang BY, Francesco M, De Rooij MFM, et al. Egress of CD19+CD5+ cells into peripheral blood following treatment with the BTK inhibitor ibrutinib in mantle cell lymphoma patients. Blood. 2013;122(14):2412-24.
27. Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 1999;17:1244-1253.
28. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-586.
29. Thall PF, Simon R, and Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Statistics in Medicine. 1995;14: 357-379.
30. Kaplan EL and Meier P. Non-parametric estimation from incomplete observations. Journal of the American Statistical Association. 1958;53:457-481