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TITLE: PHASE II STUDY OF IBRUTINIB IN PATIENTS WITH SYMPTOMATIC, PREVIOUSLY UNTREATED WALDENSTROM'S MACROGLOBULINEMIA, AND IMPACT ON TUMOR GENOMIC EVOLUTION USING WHOLE GENOME SEQUENCING.

Sponsor #: PCYC 20133

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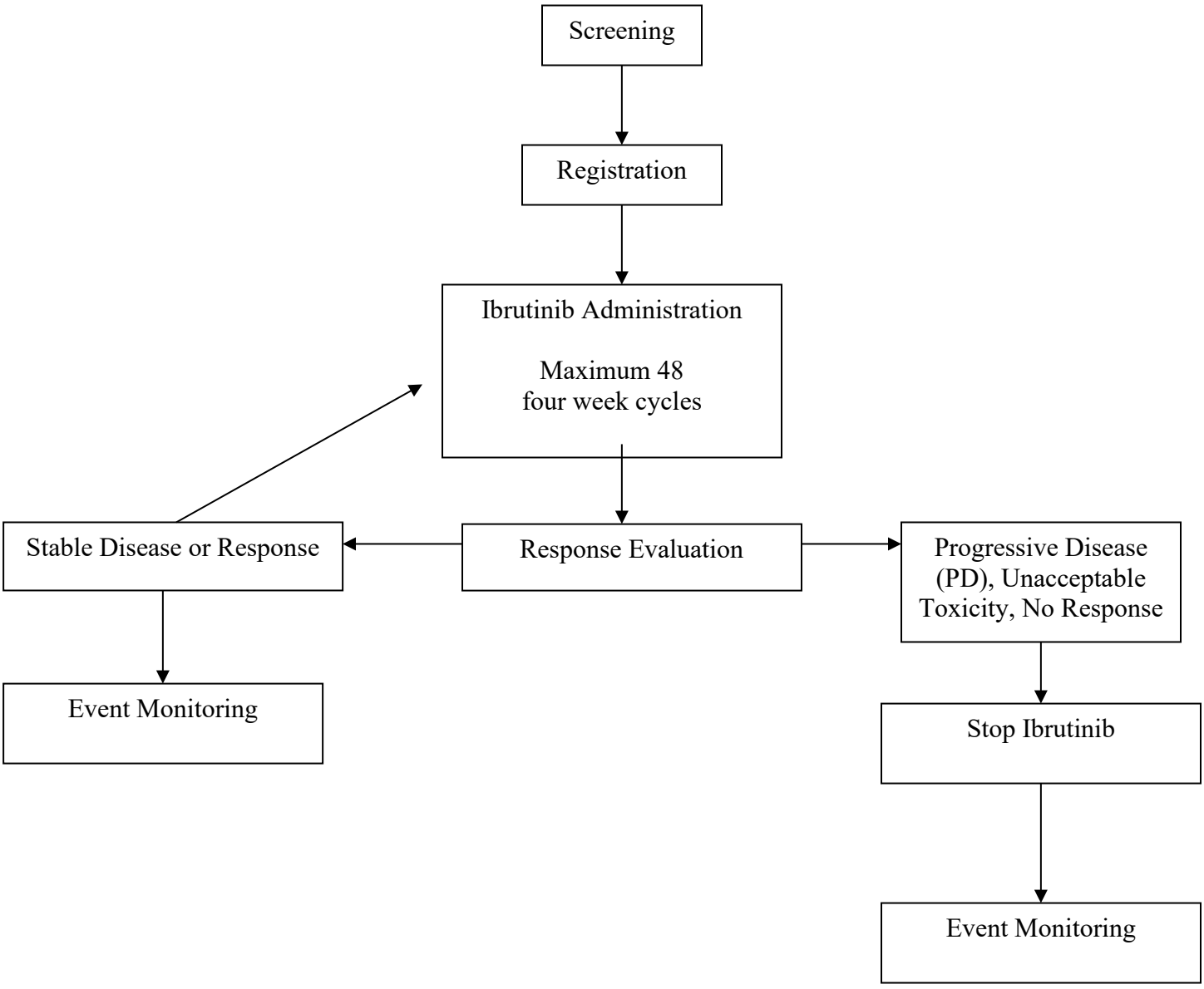
SCHEMA


Screening
Registration
Ibrutinib Administration
Maximum 48
four week cycles
Response Evaluation
Stable Disease or Response
Event Monitoring
Progressive Disease
(PD), Unacceptable
Toxicity, No Response
Stop Ibrutinib
Event Monitoring

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1. OBJECTIVES

1.1 Study Design

This is a Phase II, single center study designed to evaluate the safety and efficacy of Ibrutinib (formerly PCI-32765) in previously untreated, symptomatic Waldenstrom's Macroglobulinemia patients. Treatment will be administered in 4-week cycles to participants with WM, and participants will receive treatment until progression or upwards to 48 4-week cycles on this study. Treatment will consist of ibrutinib administered at 420 mg by mouth daily, with permitted dose modification for toxicity as per Table 6-1.

A Screening visit will be conducted within 30 days of Cycle 1, Day 1 of study drug administration. If the Screening visit and screening laboratories are done within 30 days of Cycle 1, Day 1, then a separate visit and laboratories will not be required on Cycle 1, Day 1, and will be done only at the investigator's discretion. At the Screening visit, a medical history will be obtained and a complete physical examination will be performed including vital signs, and an ECOG performance status will be assessed. A bone marrow aspirate and biopsy, and CT scanning of the chest, abdomen and pelvis will be done during screening within 90 days prior to Cycle 1, Day 1. Clinical laboratory tests including a complete blood count plus differential, comprehensive chemistry panel (electrolytes, BUN, creatinine, albumin, total protein, total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase), beta 2-microglobulin, serum and protein electrophoresis with quantification of immunoglobulins (IgM, IgG, IgA), serum free light chains, and immunofixation studies, peripheral flow cytometry lymphoma panel, coagulation panel and serum pregnancy tests for women of child-bearing potential will also be performed at the Screening visit.

Participants who meet the eligibility requirements as assessed at the Screening visit will be enrolled in the study and initiated on study drug. Participants will be evaluated for response and tolerability on the first day of each cycle (4 weeks ± 5 days) at cycles 2 and 3, and thereafter every 3 cycles (12 weeks ± 2 weeks) for the duration of protocol therapy. Participants will be eligible to continue therapy so long as they do not demonstrate progressive disease, are non-responsive and have persistent symptoms, or experience unacceptable toxicity. Modified response criteria from

the Third International Workshop on Waldenstrom's macroglobulinemia (Anderson et al, 2012) will be used to assess response, stable disease, and progressive disease according to Section 9. Response outcomes to be determined will include the best overall response rate (ORR) which includes minor responses (MR), partial responses (PR), very good partial responses (VGPR) and complete responses (CR); and best major response rate which includes PR, VGPR, and CR; landmark analyses for 2 and 4 year progression free survival; and median time to progression (TTP).

1.2 Primary Objectives

- To determine major response rates and best overall response rates of ibrutinib in previously untreated and symptomatic WM patients.

1.3 Secondary Objectives

- To assess the safety and tolerability of ibrutinib in previously untreated and symptomatic WM patients.
- Duration of response (DOR), time to response (TTR), progression-free survival (PFS) and overall survival (OS) in previously untreated, and symptomatic WM patients.
- To identify genomic variants associated with ibrutinib response, response duration and acquired resistance, including evolution of subclonal variants present at baseline.

2. BACKGROUND

2.1 Study Disease(s)

Waldenström's macroglobulinemia (WM) is a distinct clinicopathological entity of B lymphocytes that show maturation to plasma cells constituting a pathognomonic bone marrow lymphoplasmacytic infiltrate, and synthesizing IgM (Waldenström, 1986). This condition is considered to correspond to the lymphoplasmacytic lymphoma (Owen et al, 2003) as defined by the World Health Organization (WHO) classification systems (Harris et al, 1999; Swerdlow et al, 2008). The disease was first reported by Jan Waldenström, who described two patients with a high level of macroglobulin, i.e. pentameric immunoglobulin M (IgM), marked hyperviscosity with typical funduscopic picture and lymphocytoid bone marrow infiltration (Waldenström, 1944). Current frontline therapeutic options include alkylator agents, proteasome inhibitors, monoclonal antibodies, nucleoside analogues, alone

and in combination (Anderson et al, 2012; Dimopoulos et al, 2014). Response rates are higher with combination therapies (70-90%), with median progression-free survival estimates of 2-4 years. Both short and long term-toxicities impact prolonged use and re-use of many of these therapies and include risk of secondary malignancies and myelodysplasia (alkylators, nucleoside analogues), disease transformation (nucleoside analogues), moderate to severe peripheral neuropathy (proteasome inhibitors), IgM flare leading to symptomatic hyperviscosity and IgM related morbidity (rituximab), depletion of uninvolved immunoglobulins leading to increased infection risk (proteasome inhibitors, nucleoside analogues, rituximab), and immunosuppression (nucleoside analogues, alemtuzumab) (Dimopoulos et al, 2014). Therefore, novel treatment options are urgently needed for use in the primary therapy of WM patients.

Whole genome sequencing has revealed activating somatic mutations in MYD88 (L265P) and the C-terminal domain of CXCR4 in Waldenström's macroglobulinemia (Treon et al, 2012; Hunter et al, 2014). In tumor cells, $MYD88^{L265P}$ triggers NFkB activation via two divergent pathways involving Bruton's tyrosine kinase (BTK) and IRAK1/IRAK4 (Yang et al, 2013). Ibrutinib is an orally administered, small molecule inhibitor of BTK, which triggers apoptosis of $MYD88^{L265P}$ expressing Waldenstrom's macroglobulinemia cells (Yang et al, 2013). Clinical activity was observed in a small subset of Waldenstrom's macroglobulinemia patients included in a Phase I study of ibrutinib (Advani et al, 2013). Activating CXCR4 somatic mutations in Waldenström's macroglobulinemia are similar to germline mutations found in WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome patients (Hunter et al, 2013). At least 30 different $CXCR4^{WHIM}$ somatic mutations are present in Waldenström's macroglobulinemia (Treon et al, 2014). Tumor cells engineered to express $CXCR4^{WHIM}$ mutations show enhanced activation of pro-survival factors AKT and ERK, and decreased *in vitro* ibrutinib-related apoptosis (Cao et al, 2014; Rocarro et al, 2014; Cao et al, 2015).

A prospective, multicenter Phase II study examined the activity of ibrutinib in subjects with symptomatic WM disease who received at least one prior therapy (Treon et al, 2015). Ibrutinib (420 mg) was orally administered daily until progression or unacceptable toxicity. Sixty-three subjects with a median of 2 (range 1-9) prior therapies, 40% of whom were refractory to their

previous therapy were treated on this study. Post-therapy, median serum IgM levels declined from 3,520 to 880 mg/dL; hemoglobin rose from 10.5 to 13.8 g/dL, and bone marrow involvement declined from 60% to 25% ($p<0.01$ for all comparisons). Median response time was 4 weeks. Overall and major response rates were 90.5% and 73.0%, and were highest in patients with $MYD88^{L265P}CXCR4^{Wild\text{-}Type\ (WT)}$ (100% and 91.2%), followed by $MYD88^{L265P}CXCR4^{WHIM}$ (85.7% and 61.9%), and $MYD88^{WT}CXCR4^{WT}$ (71.4% and 28.6%). The 2-year progression-free and overall survival rates for all patients were 69.1% and 95.2%, respectively. Overall toxicity was moderate in this study. Grade $\geq$2 treatment-related toxicities included neutropenia (22.2%) and thrombocytopenia (14.3%) that were more common in heavily pre-treated patients; post-procedure bleeding (3.2%) prior to an amendment requiring hold on treatment for procedures; epistaxis associated with fish oil supplements (3.2%); and atrial fibrillation associated with previous arrhythmia history (3.2%) which resolved after drug hold, and did not prevent restart of therapy. Serum IgA and IgG levels were unchanged, and treatment-related infections were infrequent. These findings led to a breakthrough designation, and full approval of ibrutinib by the U.S. FDA for use in symptomatic WM patients, and adoption on NCCN guidelines. Despite the approval of ibrutinib in patients with symptomatic WM disease (regardless of previous therapy status), there is no efficacy or safety data on the use of ibrutinib as primary therapy in WM.

2.2 IBRUTINIB

Ibrutinib (formerly referred to as PCI-32765) is a selective, irreversible inhibitor of Bruton's Tyrosine Kinase (BTK). The irreversible inhibitory effect of ibrutinib on BTK activity is attributed to an electrophilic group on the molecule that binds covalently to a specific cysteine (Cys 481) in the active site of BTK. Ibrutinib is a potent inhibitor of BTK activity with a median inhibitory concentration in a cell-free system of 0.46 nM. Ibrutinib PO Hard Gelatin Capsule, the drug product intended for oral administration, contains micronized ibrutinib, microcrystalline cellulose (National Formulary [NF]), croscarmellose sodium (NF), sodium lauryl sulfate (NF), may contain magnesium stearate (NF).

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 patients with17p deletion or a TP53 mutation, and 3) patients with symptomatic WM (Treon et al, 2015).

Ibrutinib pharmacokinetics

Following oral administration of ibrutinib at doses 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

Clinical experience with ibrutinib

Ibrutinib is an orally administered agent. The first human Phase 1 study (PCYC-04753) was designed to evaluate the initial safety, tolerability, and pharmacokinetic and pharmacodynamic properties of ibrutinib in participants with recurrent B cell lymphoma. In this clinical setting a useful adverse event profile was obtained, while balancing the risk/benefit considerations.

Ibrutinib has been under investigation in ongoing or completed clinical studies in subjects with recurrent B-cell lymphoma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), prolymphocytic leukemia, and WM. Responses have been observed in all histologies treated to date, including CLL/SLL, MCL, DLBCL, and WM.

The seven ongoing and completed clinical studies of ibrutinib are summarized in the Investigator Brochure. These included two dose-finding Phase 1 studies (PCYC-04753 and PCYC-1102-CA), two Phase 2 studies using a fixed continuous dose of ibrutinib (Studies PCYC-1104-CA and PCYC-1106- CA), two studies combining ibrutinib with chemotherapy (Studies PCYC-1108-CA and CYC-1109-CA), and an extended-treatment rollover safety study for subjects who had participated in previous studies with ibrutinib (Study PCYC-1103-CA). Across all studies, malignancies under investigation include B-cell lymphoma, CLL, SLL, MCL (including both bortezomib-pretreated and bortezomib-naive), DLBCL (including activated B cell-like and germinal cell B cell-like subtypes), and pro-lymphocytic leukemia. One study is closed to enrollment and 6 are currently enrolling subjects. As of the data cutoff for this analysis, safety data are available for 392 subjects treated with ibrutinib in a Pharmacyclics-sponsored trial: 312 subjects receiving ibrutinib monotherapy and 80 subjects receiving ibrutinib in combination with 1 or more marketed chemotherapeutic agents.

In December 2011, Pharmacyclics entered into a development partnership with Janssen Research and Development for the continued development and commercialization of ibrutinib. Based on results from completed and ongoing clinical trials, future development plans include the initiation of additional clinical trials in CLL/SLL, NHL, and multiple myeloma. Phase 3 studies in CLL/SLL, MCL and WM are currently in progress.

PCYC-04753 Study

A multicenter Phase 1 study in subjects with relapsed or refractory NHL including CLL and WM was the first in-human trial of ibrutinib. The objectives included studying the safety profile of ibrutinib, identifying the maximum tolerated dose (MTD) and optimal dosing schedule, and

characterizing efficacy, pharmacokinetics, and pharmacodynamics. A minimum of 6 subjects per cohort received 1 of 5 escalating dose levels of ibrutinib between 1.25 and 12.5 mg/kg for 28 consecutive days in a 35-day cycle, with the objective of escalating 3 dose levels above that which achieved full BTK occupancy based on the fluorescent probe assay. Two additional cohorts received a continuous ibrutinib dose of 8.3 mg/kg without a 7-day rest and a fixed continuous dose of 560 mg/day.

Summary of Safety Data from PCYC-04753 and Monotherapy Trials

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 IB.

Clinical Efficacy

The outcome of patients with B-cell malignancies on ibrutinib have been published (Advani et al, 2012). Responses have been observed in all histologies dosed to date, including CLL/SLL, MCL, DLBCL and WM who received ibrutinib treatment at dose up to 560 mg a day. Among 50 evaluable subjects across all B-cell histologies, Advani et al (2012) reported an overall response rate of 60%, with 7 complete responses (CRs) and 23 partial responses (PRs). A fluorescent probe

assay demonstrated complete active-site occupancy of BTK by ibrutinib in subjects given doses of 2.5 mg/kg or higher.

Another recent report presented efficacy results from 10 subjects with relapsed/refractory DLBCL receiving a fixed continuous dose of 560 mg/day (Staudt et al, 2011). All subjects had Stage IV disease and had received a median of 3 previous therapeutic regimens (range: 1, 6). Two subjects achieved a CR and 1 subject a PR, for an overall response rate of 30%. An additional 3 subjects displayed stable disease with 13, 15, and 21 weeks on treatment. The trial continues to enroll subjects with DLBCL into the final cohort using a continuous fixed dose of 560 mg/day.

A multicentre, prospective study of single agent ibrutinib investigated the safety and efficacy of ibrutinib in relapsed or refractory WM patients (Treon et al, 2015). The median number of prior therapies for these patients was 2 (range 1-9), and 40% of patients were refractory to their previous therapy. Seventy-eight percent of patients had a moderate-high WM IPSS prognostic score. Post therapy, the median serum IgM levels for all 63 patients declined from 3,520 to 880 mg/dL at best response ($p<0.01$). Pre-therapy, 46/63 (73.0%) patients had a serum IgM $\geq$3,000 mg/dL; following treatment, at best response, 6/63 (9.5%) patients had a serum IgM $\geq$3,000 mg/dL ($p<0.01$). Median BM involvement decreased from 60% to 25% ($p<0.01$), while hemoglobin increased from a median of 10.5 to 13.8 g/dL at best response ($p<0.01$). Responses included very good partial response (n=10); partial response (n=36); and minimal response (n=11) for overall and major responses of 90.5% (95% CI 80.4%-96.4%) and 73.0% (95% CI 60.3-83.4%), respectively. The median time to at least minor and partial responses were 4 and 8 weeks, respectively. Overall responses were similar regardless of baseline age (<65 vs. $\geq$65 years), ECOG status (0 vs. $\geq$1), pre-therapy Waldenström's macroglobulinemia International Prognostic Scoring System (IPSS) score, serum β_2-microglobulin levels (<3.0 vs. >3.0 mg/L), hemoglobin (<11 vs. >11 g/dL), serum IgM (<4,000 vs. $\geq$4,000 mg/dL), BM disease involvement (<50% vs. $\geq$ 50%), prior relapsed or refractory status, and prior lines of therapy (1-3 vs. >3), as well as for major responses across most of the baseline subgroups (Treon et al, 2015). Overall and major response rates were highest in patients with $MYD88^{L265P}CXCR4^{WT}$ (100% and 91.2%), followed by $MYD88^{L265P}CXCR4^{WHIM}$ (85.7% and 61.9%), and $MYD88^{WT}CXCR4^{WT}$ (71.4% and 28.6%). Overall and major response

rates improved with prolonged therapy (>6 cycles) in patients with $MYD88^{L265P}CXCR4^{WT}$ and $MYD88^{L265P}CXCR4^{WHIM}$, with more pronounced improvements occurring for the latter. Best serum IgM and hemoglobin responses were also impacted by tumor genotype, with improvements most evident in patients with $MYD88^{L265P}CXCR4^{WT}$, and least in those with $MYD88^{WT}CXCR4^{WT}$.

CT-defined adenopathy (≥1.5 cm) was present in 37 patients at baseline. Serial imaging for 35 patients showed decreased or resolved (n=25; 67.6%); stable (n=9; 24.3%); or increased (n=1; n=2.9%) adenopathy. Two patients came off study before repeat imaging was required. Among 7 patients with CT-defined splenomegaly (≥15 cm), spleen size was decreased (n=4; 57.1%), stable (n=2; 28.6%), or not evaluable (n=1; 14.3%) following elective splenectomy. Nine patients (14.3%), 3 with positive anti-MAG antibodies, received ibrutinib for progressive IgM-related peripheral sensory neuropathy. All responded, and subjective improvements in peripheral sensory neuropathy occurred in 5, and remained stable in 4 during the treatment course. Symptomatic hyperviscosity related to progressive disease that required plasmapheresis prompted start of ibrutinib in 4 patients. All responded, and none required additional plasmapheresis by the end of Cycle 2. One patient required plasmapheresis for acquired Factor VIII deficiency. He responded, and did not require further plasmapheresis. The spontaneous bleeding events that prompted therapy also resolved. With a median on treatment duration of 19.1 (range 0.5-29.7) months, 43 patients (68.3%) remained on therapy. Reasons for treatment discontinuation included non-response (n=1); progressive disease (n=7); treatment-aggravated thrombocytopenia (n=1); hematoma after BM biopsy (n=1); prolonged drug hold for infection unrelated to ibrutinib (n=1); myelodysplasia/acute myeloid leukemia associated with baseline 5q- deletion related to prior therapies (n=1); disease transformation possibly related to prior nucleoside analogue therapy (n=2); antineoplastic therapy for rectal carcinoma (n=1); ibrutinib incompatible medication (n=1), patient decision to use commercially sourced ibrutinib (n=2), travel difficulties (n=1), and alternative therapy (n=1). The estimated progression-free and overall survival at 24 months was 69.1% (95% CI 53.2%-80.5%) and 95.2% (95% CI 86.0-98.4%), respectively. For patients with progressive disease, the median time to progression was 9.6 (range: 3.5 – 19.4) months if transformation cases were censored, and 9.5 (range: 3.5 – 19.4) months if transformation events were included. Subset analysis showed that

>3 prior lines of therapy, high pre-therapy IPSS score, and $MYD88^{WT}CXCR4^{WT}$ mutation status associated with inferior progression-free survival.

2.3 Rationale

In WM cells, $MYD88^{L265P}$ triggers NFkB activation via two divergent pathways involving Bruton's Tyrosine Kinase (BTK) and IRAK1/IRAK4 (Yang et al, 2013). *In vitro*, the BTK inhibitor ibrutinib has shown selective pro-apoptotic effects on $MYD88^{L265P}$ expressing WM cell lines and primary patient cells. (Yang et al, 2013). Activating CXCR4 somatic mutations in WM are the first ever reported in cancer, and are similar to germline mutations found in WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome patients (Hunter et al, 2014). At least 30 different $CXCR4^{WHIM}$ somatic mutations are present in untreated WM patients including non-sense and frameshift mutations (Treon et al, 2014). WM cells engineered to express $CXCR4^{WHIM}$ mutations show enhanced activation of pro-survival factors AKT and ERK, and decreased *in vitro* ibrutinib-related apoptosis (Cao et al, 2014a; 2014b). Ibrutinib as a single agent has been evaluated in previously treated WM patients. Advani et al (2012) observed responses in 3 of 4 WM patients in a Phase I study. In a prospective multicenter study, 63 patients with relapsed or refractory disease received single agent ibrutinib. Overall and major response rates were 90.5% and 73.0%, and were highest in patients with $MYD88^{L265P}CXCR4^{Wild\text{-}Type\ (WT)}$ (100% and 91.2%), followed by $MYD88^{L265P}CXCR4^{WHIM}$ (85.7% and 61.9%), and $MYD88^{WT}CXCR4^{WT}$ (71.4% and 28.6%). The median time to response was 4 weeks, and the 2-year progression-free and overall survival rates for all patients were 69.1% and 95.2%, respectively. Treatment was well tolerated, with manageable adverse events. Heavily pre-treated patients were more at risk for significant neutropenia and thrombocytopenia. No significant declines in uninvolved immunoglobulins (serum IgA, IgG) were observed over the course of therapy. Taken together, the above findings suggest that: i) treatment with ibrutinib is likely to produce high overall (85-90%) and major (70%) response rates that are at least as comparable to best current frontline WM therapy regimens; ii) treatment with ibrutinib is likely to produce more rapid responses (4 weeks) versus current WM frontline therapy (>8 weeks to 24 weeks); and iii) treatment with ibrutinib is likely to be as well tolerated, and with less adverse impact on blood counts and uninvolved immunoglobulin levels compared to many current frontline treatment options for WM.

2.4 Correlative Studies Background

Whole genome sequencing has revealed MYD88 L265P and CXCR4 WHIM-like somatic mutations as the most common variants in untreated WM patients, with their presence in 95% and 35% of patients (Treon et al, 2012; Hunter et al, 2014; Treon et al, 2014). MYD88 L265P triggers activation of BTK, the target of ibrutinib (Yang et al, 2013). CXCR4 is a receptor that responds to SDF-1a ligand stimulation, and mediates trafficking of WM cells to the BM microenvironment. Both nonsense (leading to protein truncation) and frameshift CXCR4 WHIM-like somatic mutations have been described in WM patients which impact the regulatory C-regulatory domain of CXCR4, and lead to hyper-activation of AKT and ERK in response to SDF-1a activation (Cao et al, 2014a; 2014b). WM cells engineered to express nonsense and frameshift CXCR4 mutant receptors show resistance to ibrutinib, which is in part mediated by AKT and ERK (Cao et al, 2014a). Use of plerixafor, an FDA approved antagonist of CXCR4, sensitized CXCR4 WHIM mutated cells to the effects of ibrutinib. CXCR4 WHIM mutations are typically subclonal, and the clonal distribution varies considerably among WM patients (Treon et al, 2014; Xu et al, submitted).

The genomic events associated with ibrutinib response and acquired resistance requires further clarification in WM patients. Several somatic mutations in patients with CLL with acquired resistance to ibrutinib have been reported (Woyach et al, NEJM 2014). Their studies identified a cysteine-to-serine mutation in BTK at the binding site of ibrutinib in five patients (BTK^{C481S}) as well as three distinct mutations in PLCγ2 in two patients. Functional analysis showed that the C481S mutation of BTK results in a protein that is only reversibly inhibited by ibrutinib. The R665W and L845F mutations in PLCγ2 were postulated to be gain-of-function mutations that lead to autonomous B-cell-receptor activity. These mutations were not found in any of the patients with prolonged lymphocytosis who were taking ibrutinib.

Importantly, their presence (at a subclonal level) at baseline was demonstrated in these studies. Knowledge of somatic variants associated with ibrutinib response and acquired resistance may provide both predictive markers, and lead to treatment advances. The use of whole genome sequencing (WGS) with deep map read coverage (≥120 X) provides the opportunity to interrogate

clonal and subclonal genomic events. Deep WGS performed at baseline, and at 6, 12, 24, 36, and 48 months will provide the opportunity to interrogate baseline and evolving genomic events in response to treatment.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Clinicopathological diagnosis of Waldenstrom's Macroglobulinemia and meeting criteria for treatment using consensus panel criteria from the Second International Workshop on Waldenstrom's macroglobulinemia (Kyle et al, 2003).

3.1.2 Measurable disease, defined as presence of serum immunoglobulin M (IgM) with a minimum IgM level of $\geq$ 2 times the upper limit of normal is required.

3.1.3 Age $\geq$ 18 years.

3.1.4 ECOG performance status $\leq$2 (see Appendix A.).

3.1.5 Participants must have normal organ and marrow function as defined below:

- Absolute neutrophil count $\geq$ 1,000/μL
- Platelets $\geq$ 50,000/μL
- Total bilirubin $\leq$ 2.0. mg/dL or < 2.5 mg/dL if attributable to hepatic infiltration by neoplastic disease or Gilbert's syndrome.
- AST (SGOT) and ALT (SGPT) $\leq$ 2.5 X institutional upper limit of normal
- Estimated Creatinine Clearance ≥30ml/min

3.1.5.1 Not on any active therapy for other malignancies with the exception of topical therapies for basal cell or squamous cell cancers of the skin.

3.1.5.2 Females of childbearing potential (FCBP) must agree to use two reliable forms of contraception simultaneously or have or will have complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) while participating in the study; and 2) for at least 28 days after discontinuation from the study. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. FCBP must be referred to a qualified provider of contraceptive methods if needed.

3.1.6 Able to adhere to the study visit schedule and other protocol requirements.

3.1.6.1 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Prior systemic therapy for WM

3.2.2 Any serious medical condition, laboratory abnormality, uncontrolled intercurrent illness, or psychiatric illness/social condition that would prevent the participant from signing the informed consent form.

3.2.3 Concurrent use of any other anti-cancer treatments or any other investigational agents.

3.2.4 Concomitant use of warfarin or other Vitamin K antagonists.

3.2.5 Concomitant treatment with strong CYP3A4/5 inhibitor.

3.2.6 Any condition, including the presence of laboratory abnormalities, which places the participant at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

3.2.7 Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion could interfere with the absorption or metabolism of ibrutinib.

3.2.8 Known CNS lymphoma.

3.2.9 Currently active, clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification, or history of myocardial infarction, unstable angina or acute coronary syndrome within 6 months of screening.

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

3.2.11 Known history of Human Immunodeficiency Virus (HIV), active infection with Hepatitis B Virus (HBV), and/or Hepatitis C Virus (HCV). 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.

3.2.12 Lactating or pregnant women.

3.2.13 Inability to swallow capsules.

3.2.14 History of non-compliance to medical regimens.

3.2.15 Unwilling or unable to comply with the protocol.

3.2.16 Major surgery within 4 weeks of first dose of study drug.

3.2.17 No active infections requiring systemic therapy.

3.2.18 Known bleeding disorders with the exception of acquired Von Willebrand Disorder suspected on the basis of WM.

3.2.19 History of stroke or intracranial hemorrhage within 6 months prior to enrollment.

3.2.20 Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix B)

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS)

OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

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

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for ibrutinib are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial anti-neoplastic agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1 Treatment Regimen

Participants will be treated with oral ibrutinib daily for a maximum of 48 four week cycles. Upon completion of the 48 cycles, participants may transition to receive commercial ibrutinib at the discretion of the investigator. They will be requested to maintain a medication diary of each dose of study medication. The medication diary will be returned to clinic staff at the subsequent visit.

Agent	Dose	Schedule	Cycle Length
Ibrutinib	420mg	PO QD	28 days (4 weeks)

5.2 Pre-Treatment Criteria

C1D1 results need to meet eligibility parameters. Day 1 chemistry and hematology laboratories must be reviewed prior to treatment.

Participants must meet the following criteria on Day 1 of cycles (except for Cycle 1, Day 1) with clinic visits (i.e. 2, 3, 6, 9, etc.):

- No grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal thearpy)
- No grade 4 or unmanageable nonhematologic grade 3 toxicities
- Neutrophil count >/=500/μL
- In subjects without baseline thrombocytopenia:
    - Platelet count >/= 50,000/μL in the presence of bleeding
    - Platelet count >/= 25,000 μL without bleeding
- In subjects with baseline thrombocytopenia:
    - Platelet count decrease <75% or >/= 20,000/ μL, whichever is higher without bleeding
    - Platelet count decrease <50% in the presence of bleeding

5.3 Agent Administration

Ibrutinib 420 mg (made up of three 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.

If a dose is not taken at the scheduled time, it can be taken as soon as possible within 6 hours, with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

Ibrutinib will be dispensed to subjects in the original 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.

Participants will be treated for up to 48 cycles or until progression, unacceptable toxicity, or decision to withdraw from the trial. Dose reductions due to toxicity will be permitted on information seen in Table 6-1.

Ibrutinib will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken. Participants will be instructed to take the study drug at approximately the same time each day, ideally at least 30 minutes before eating or at least 2 hours after a low fat meal. Participants will also be instructed on how to complete the diary. Participants will be reminded that dietary habits around the time of ibrutinib intake should be as consistent as possible throughout the study. If a dose is missed, study drug may be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, ibrutinib should not be taken on that date, and the patient should take the next ibrutinib dose at the scheduled time the next day. The missed dose will not be made up and must be returned at the next scheduled visit. The patient will be instructed to document missed drug doses in the study diary. Furthermore, they will be instructed to call the PI or research nurse if vomiting occurs. If the pills are vomited, this should be noted on the patient diary, but a replacement dose should not be taken that day. All dosages prescribed and dispensed to the participant, and all dose changes during the study must be recorded.

One cycle of ibrutinib is once daily, oral administration for 4 weeks. At each study visit, enough ibrutinib will be dispensed until the next cycle. For visits occurring monthly (every 4 weeks ± 5 days), one cycle of pills will be dispensed. For visits occurring every 12 weeks ± 2 weeks), three cycles of pills will be dispensed. In the event of inclement weather or other circumstances that prevent a patient from coming to clinic, the principal investigator may permit up to 4 week supply of drug to be sent to the patient by a trackable delivery service, and receipt confirmed. A log book of such emergency supplies shall be kept by the study team that will include shipping information, telephone log confirming receipt, and reason that emergency supply was dispatched to the subject.

Drug accountability will be done at each study visit; unused drug and diaries will be collected from the participant, unused drug will be counted and returned to the pharmacy to be destroyed. A new prescription for either one cycle or three cycles, as detailed above, will be filled by the participant, and they will be given a new diary at each visit. In some circumstances, when it is unclear at a visit if a patient is to continue on to the next cycle (i.e. in the event of suspected but not confirmed progression), then the participant will be allowed to continue on their current supply of drug and diary use. Drug and diary may then be sent to the patient by a trackable delivery service, with receipt confirmed, if it is later determined that the participant is eligible to continue with study drug. In some circumstances, it may be necessary to provide a participant an interim supply of drug and diary. In such circumstances, interim drug supply may be provided or sent to the patient, but such supply and supplementary diary should not exceed 4 weeks supply of drug.

Medication labels will comply with US legal requirements and be printed in English. The storage conditions for study drug will be described on the medication label. Ibrutinib will be provided by Pharmacyclics LLC. Ibrutinib is formulated as capsules for oral administration and will be available for this study in 140mg capsules.

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 7 for further information regarding AE reporting

5.4 General Concomitant Medication and Supportive Care Guidelines

Participants will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the participant about any new medications he/she is or has taken after the start of the study drug.

Anti-emetics are permitted if clinically indicated. Standard supportive care medications are permitted. All concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to study drug start and for the duration of study treatment, including physical therapy and blood transfusions, should be recorded. The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to participants.
- No other anti-cancer therapy including radiation therapy should be given to participants. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Growth factors (i.e. G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically, including to establish eligibility, but may be prescribed at the discretion of the treating physician for treatment-related hematologic events in accordance with ASCO guidelines, and to meet re-treatment criteria. They may be given on the same day to establish re-treatment criteria
- Concomitant use of anti-platelet agents and anticoagulants:
    - Laboratory studies have shown that, in vitro, ibrutinib can prevent platelets from aggregating normally; the clinical significance of this finding is unknown at this time. While serious bleeding has been uncommon in participants treated to date, it is possible that treatment with the study drug could increase the risk of bruising or bleeding, particularly in participants receiving other anti-platelet agents or anticoagulants. Participants receiving anti-platelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising, and ibrutinib should be withheld in the event of any grade 2 or higher bleeding events

until complete resolution to < grade 1. Participants with any grade CNS bleeding will have treatment held. If the CNS bleeding event is attributed to ibrutinib therapy, then treatment will be discontinued. If the CNS bleeding is attributed to other causes (i.e. trauma), then treatment will be held until resolution, at which time ibrutinib can be re-started. Participants on anticoagulants with CNS bleeding events must discontinue anticoagulation prior to re-starting ibrutinib. Participants may resume at previous dose level.

  - Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib.
  - 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.
  - Supplements such as fish oils 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.

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 5.4).

- 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 X. 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.

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.

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

No chronic treatment with systemic steroids (at dosages equivalent to prednisone > 20 mg/day for more than 14 days) or other immunosuppressive agents should be used. Topical or inhaled corticosteroids are allowed.

Table 5.1 Inhibitors and Inducers of CYP3A4/5

Inhibitors of CYP3A4/5 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:

- A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance. Strong inhibitors are capitalized in the list below.
- A moderate inhibitor is one that causes a >2-fold increase in plasma AUC values or 50-80% decrease in clearance.
- A weak inhibitor is one that causes a >1.25-fold but <2-fold increase in plasma AUC values or 20-50% decrease in clearance.

Inhibitors of CYP3A4/5	**Inducers of CYP3A4/5**
Strong inhibitors:	Carbamazepine
INDINAVIR	Efavirenz
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbarzepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
TELITHROMYCIN	Pioglitazone
Moderate inhibitors:	Rifabutin
aprepitant	Rifampin
erythromycin	St. John's Wort
diltiazem	Troglitazone
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

5.5 Guidelines for Ibrutinib Management with Surgeries or Procedure

Ibrutinib may increase the risk of bleeding with invasive procedures or surgery. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib. The treating investigator should use the below guidance for surgical procedures that they determine requires withholding ibrutinib.

Surgical Procedures

Consider the benefit-risk of withholding ibrutinib for 3 to 7 days pre and post-surgery, depending upon the type of surgery and the risk of bleeding.

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.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Patients will receive therapy on study for 48 four week cycles. Afterwhich patients may elect to transition to commercial supply. In the absence of treatment delays due to adverse events, treatment may continue for 48 four week cycles while on study or until one of the following criteria applies:

- Confirmed disease progression or development of new signs or symptoms of disease;
- Lack of response to signs or symptoms that prompted therapy after 12 weeks of therapy (defined as non-responder);
- Commencement of new anti-neoplastic therapy (including radiation therapy) for WM or other malignancy including myelodysplasia or WM disease transformation;
- Intercurrent illness or hold of study drug for any other reason for > 28 days, unless allowed to re-start at the discretion of the treating investigator if toxicity does not recur and is fully resolved;
- Unacceptable adverse event(s);
- In the study teams opinion, participant has demonstrated an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements;
- Participant decides to withdraw from the study;

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Special mentions:

For participants meeting criteria for disease progression (based on consensus panel criteria for IgM response) but are deemed by the investigator to be clinically benefiting from ibrutinib, these individuals will be permitted to continue on protocol therapy at the principal investigator's discretion. Documentation describing the rationale for continuing benefit shall be entered into the medical record. Clinical benefit will be determined by considering clinical data, such as overall participant performance and disposition, complete blood counts, and when necessary, results from bone marrow biopsies and/or CT scans. In such instances any new nadir that may result with continued therapy will be used as the study nadir point for this patient. Since serum IgM levels are known to increase with drug holds with ibrutinib (Treon et al, 2015), serum IgM levels for patients holding study drug >3 days will be considered non-evaluable. Patients must be on $\geq$ 2 consecutive weeks of therapy for determination of a reliable IgM reading for response or progression assessment purposes.

Participants will be removed from the protocol therapy when any of the above criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the principal investigator: Steven P. Treon MD, PhD at 617-632-2681.

5.7 Duration of Follow Up

Participants will be followed for up to two years after removal from or completion of the

study, until new treatment or death, whichever occurs first. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, unless the event is irreversible.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- 2 years of follow-up is completed
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A QACT Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.). All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted. If administration of ibrutinib must be interrupted because of unacceptable toxicity,

drug dosing will be interrupted or modified according to rules described in Table 6-1.

Dose re-escalations will not be permitted once dose reduced to next lower dose level. Dose reductions are permitted down to dose level -2 in Table 6-1 before a patient is taken off study. If a participant requires a dose delay for > 28 days, then the participant will be permitted to resume study treatment at the discretion of the treating investigator IF toxicity does not recur and is fully resolved. The participant will be allowed to resume study drug at the previous dose level. If the toxicity recurs the Drug Modification/Discontinuation Actions listed below should be followed. All interruptions or changes to study drug administration must be recorded.

Table 6-1. Ibrutinib Dose Modification Guidelines

Dose Level	Dose and Schedule
1	420 mg po qD (3 x 140 mg capsules)
-1	280 mg po qD (2 x 140 mg capsules)
-2	140 mg po qD (1 x 140 mg capsule)

Dosing will be held for any of the following conditions:

- Grade 4 ANC (< 500/μL) for > 7 days. Neutrophil growth factors may be used as per ASCO guidelines (see section 5.4).
- Grade 3 Platelets (< 50,000/μL) in the presence of clinically significant bleeding events; or, in subjects with baseline thrombocytopenia, a platelet decrease of 50-74% from baseline in presence of bleeding;
- Grade 4 Platelets (< 25,000/μL) or in subjects with baseline thrombocytopenia, decrease of > 75% from baseline or < 20,000/ μL, whichever is higher;
- Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal therapy);
- Any other related grade 4 toxicities and any unmanageable non-hematologic Grade 3 toxicities.
- For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the

risks and benefits of restarting and continuing ibrutinib treatment. If clinically indicated, the use of non-warfarin or vitamin k antagonist anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (see section 5.4 for more information).

Drug Modification/Discontinuation Actions for Ibrutinib-related events

- 1st Hold. Ibrutinib will be held until recovery to baseline or grade 1 from criteria to hold, then restarted at the original dose level (420 mg daily);
- 2nd Hold. Ibrutinib will be held until recovery to baseline or grade 1 from criteria to hold, then restarted at dose level -1, i.e. 280 mg daily;
- 3rd Hold. Ibrutinib will be held until recovery to baseline or grade 1 from criteria to hold, then restarted at dose level -2, i.e. 140 mg daily;
- 4th Hold. Ibrutinib should be discontinued.

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 (Refer to Appendix B).

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine

reporting.

7.1 Expected Toxicities

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study. Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

7.1.1 Adverse Events List

7.1.1.1 Adverse Event List(s) for Ibrutinib

Risks

Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily 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 5.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 5.4 for guidance on ibrutinib management with surgeries or procedures.

Cardiac

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 6..

Cytopenias

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

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy.. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged, follow the protocol dose modification guidelines (see Section 6).

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). 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.

Non-Melanoma Skin Cancer

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

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..

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 5.

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.

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

Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 6).

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 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 30 days (or 90 days for male partners) 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.

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.

Treatment-Emergent Adverse Events in > 10% of Subjects

Treatment-emergent AEs in more than 10% of subjects receiving ibrutinib as monotherapy (N=1071) are summarized in Table 5. The most frequently reported treatment-emergent AEs were diarrhea, fatigue, nausea, cough, anemia, pyrexia, and neutropenia.

Table 5: Treatment-Emergent Adverse Events (any grade) in >10% of Subjects Receiving Ibrutinib Monotherapy including crossover patients (Safety Population)

	Monotherapy Studies
Number of Subjects	1071
Subject with 1 or more events	987 (92.2%)
Preferred Term	
Diarrhoea	429 (40.1%)
Fatigue	315 (29.4%)
Nausea	238 (22.2%)
Cough	199 (18.6%)
Anaemia	188 (17.6%)
Pyrexia	185 (17.3%)
Neutropenia	178 (16.6%)
Arthralgia	159 (14.8%)
Oedema peripheral	159 (14.8%)
Constipation	158 (14.8%)
Thrombocytopenia	158 (14.8%)
Upper respiratory tract infection	147 (13.7%)
Muscle spasms	146 (13.6%)
Vomiting	142 (13.3%)
Dyspnoea	130 (12.1%)
Headache	127 (11.9%)
Pneumonia	127 (11.9%)
Decreased appetite	120 (11.2%)
Contusion	117 (10.9%)
Dizziness	108 (10.1%)

Note: Monotherapy studies includes PCYC-1102-CA, PCYC-1104-CA, PCYC-1106-CA, PCYC-1112-CA, PCYC-1112-CA(crossover only), PCYC-1117-CA, PCYC-1118E-CA, PCYC-04753, PCI-32765-JPN-101, PCI32765MCL2001, and PCI32765CLL3001(crossover only).

[TSFAE01B.RTF] [JNJ-54179060\Z_IB\DBR_IB_2015\RE_IB_2015\PROD\TSFAE01B.SAS] 26JUN2015, 11:43

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**

- AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or up to 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.3.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

Grade 3 and 4 expected hematologic events (listed in Section 6 and the Investigator's Brochure) that have not induced clinical signs or symptoms do not require separate reporting as serious adverse events.

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

n/a IND Exempt.

7.5 Expedited Reporting to Pharmacyclics LLC (PCYC)

The overall PI, as study sponsor, will be responsible for all communications with PCYC. Reportable events to Pharmacyclics LLC are any that include the following and begin after signing consent:

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

reporting timelines.

- Major hemorrhage is defined as any of the following:
    - 1. Any treatment-emergent hemorrhagic adverse event of Grade 3 or higher.
    - 2. Any treatment-emergent serious AE of bleeding of any grade.
    - 3. Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.
    - * All hemorrhagic events requiring transfusion of RBC should be reported as Grade 3 or higher AE per CTCAE. Events meeting the definition of major hemorrhage will be captured as an event of special interest according to the above.

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakePM@pcyc.com) or fax ((408) 215-3500) to Pharmacyclics Drug Safety, or designee, within 24 hours of the event.

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Ibrutinib

8.1.1 Description

Ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has a molecular weight of 440.50 g/mole (anhydrous basis). Ibrutinib exhibited 18% to 23% oral bioavailability in rats and 7% to 11% oral bioavailability in dogs. The mean terminal half-life of ibrutinib after oral administration ranged from 1.7 to 3.1 hours in mice, 1 to 4.7 hours in rats, and 3.3 to 6.4 hours in dogs. Preliminary results suggest a 1.5- to 2.5-hour half-life of ibrutinib in humans. The effects of renal and/or hepatic impairment on drug clearance are not known at this time. In vitro studies have indicated that ibrutinib is metabolized extensively by cytochrome P450 (CYP) 3A4.

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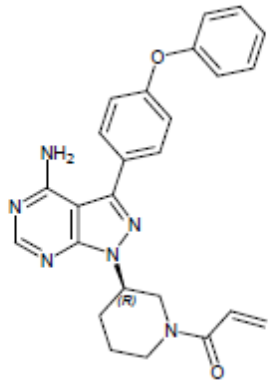
8.1.2 Form

The structure of ibrutinib is:



Ibrutinib is a white to off-white crystalline solid. Ibrutinib has a single chiral center and is the R-enantiomer. Ibrutinib product is manufactured for Pharmacyclics LLC by a contract manufacturer.

Ibrutinib PO Hard Gelatin Capsule is an oral formulation containing micronized ibrutinib and the following compendial excipients: microcrystalline cellulose (NF); croscarmellose sodium (NF); sodium lauryl sulfate (NF); may contain magnesium stearate (NF). The 140 mg strength contains 140 mg of the active ingredient, ibrutinib, adjusted for water content and purity in a size 0, gray, hard gelatin capsule. Capsules are packaged in 60-cc high-density polyethylene (HDPE) bottles

with an induction seal and a child resistant screw top cap. Each bottle is distributed by Pharmacyclics LLC. The number of capsules per bottle is indicated on the label. The HDPE bottles are labeled with the appropriate information and intended for distribution to participants. Empty HDPE bottles will not be supplied by Pharmacyclics LLC.

8.1.3 **Storage and Stability**

The recommended storage condition for ibrutinib PO Hard Gelatin Capsule is at 15°C to 25°C [59° F to 77° F] with excursions permitted to 30°C (86°F). Under these conditions, the drug product is expected to remain within specifications for at least 6 months. Total accumulative excursions between 25°C and 30°C must not exceed 12 months. Formal ICH stability studies are ongoing to determine the shelf-life of the product. Temperatures lower than 15°C or greater than 30°C must be reported to Pharmacyclics for evaluation of impact on product quality.

8.1.4 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment. If a drug shipment arrives damaged, or if there are any other drug complaints, a SAE/Product Complaint Form should be completed and faxed to Pharmacyclics Drug Safety or designee.

8.1.5 **Availability**

Ibrutinib will be supplied free-of-charge from Pharmacyclics LLC for this study.

8.1.6 **Administration**

Ibrutinib should be self-administered daily by the participant and should be taken at approximately the same time each day. Ibrutinib is intended to be administered orally once daily with 8 ounces (approximately 240 mL) of water (avoid GRAPEFRUIT JUICE and Seville Orange Juice Products due to CYP450 3A4 inhibition). The capsules should be swallowed intact and participants should not attempt to open capsules or dissolve them in water.

Each dose of ibrutinib should be taken at least 30 minutes before eating or at least 2 hours after a meal, at approximately the same time each day. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the participant should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Dietary habits around the time of ibrutinib intake should be as consistent as possible throughout the study. If the pills are vomited this should be noted on the diary, but a replacement dose should not be taken that day. A study diary will be used to aid with study drug administration compliance.

One cycle of ibrutinib is once daily, oral administration for 4 weeks ± 5 days. At each study visit, enough ibrutinib will be dispensed until the next cycle. For visits occurring monthly (every 4 weeks ± 1 week), one cycle of pills (5 weeks of ibrutinib therapy) will be dispensed. For visits occurring every 12 weeks ± 2 weeks), three cycles of pills (14 weeks) will be dispensed.

8.1.7 **Ordering**

Ibrutinib will be supplied by Pharmacyclics LLC. Participating sites will order ibrutinib directly from Pharmacyclics LLC. Ibrutinib orders will be emailed to ist.ctep@pcyc.com and referenced under the Pharmacyclics LLC study number PCYC #20133 or Protocol ID #15-359.

8.1.8 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.9 **Destruction and Return**

Unused ibrutinib capsules will be returned by the participant, collected and counted at each study visit, and will be returned to pharmacy for destruction. Unused supplies of ibrutinib will be destroyed according to institutional policies.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Laboratory Correlative Studies

Genomic and transcriptional studies

Whole genome and transcriptome studies will be performed using bone marrow aspirates (40 ml) and peripheral blood (PB) samples (4 lavender tops) that will be collected in heparinized syringes from all study participants at baseline, cycles 6, 12, 24, 36 and 48. Bone marrow (BM) and peripheral blood (PB) mononuclear cells will be isolated by density gradient centrifugation, and WM lymphoplasmacytic cells isolated from BM aspirates by $CD19^+$ selection using immunomagnetic MACS micro-beads (Miltenyi-Biotech, Auburn, CA). By previous studies, the purity of isolated B-cells ($CD19^+$) was over 90%, and median clonal B-cell population by light chain restriction was >95% by this method. CD19-depleted PBMC will be used as normal paired tissue. High molecular weight DNA will be isolated using Allprep DNA/RNA mini kit (Qiagen, Valencia, CA). Library construction and WGS of paired-end clones will be performed by Complete Genomics Inc. (CGI; Mountain View CA) as previously described. Read sequences will be aligned to reference genome NCBI Build 37. High confidence somatic variants will be identified using CGAT version 1.3 with a somatic score of 0.1, giving an estimated one false somatic single nucleotide variant per 17.7 Mb of DNA. Copy number will be estimated by %GC normalized read depth, and acquired uniparental disomy (aUPD) identified as copy-neutral loss of heterozygosity. Allele imbalance will be determined by percentage of reads mapping to the minor allele at heterozygous SNPs averaged over 100 Kb. Transcriptome studies will be performed using Illumina HiSeq platform. Gene expression will be inferred from read counts, and correlated to genomic findings and response to therapy. Categorical comparisons will be analyzed using the Fisher's exact probability test, and the Mann-Whitney U-test to evaluate ordinal comparisons. Benjamini Hochberg correction will be used for multiple comparison testing with a p-value ≤ 0.05 deemed to be significant. Calculations will be performed with R (R Foundation for Statistical Computing, Vienna, Austria). Confirmatory and additional exploratory studies may also be performed on collected DNA and RNA that are relevant to WM pathobiology and treatment outcome.

Assessment of MYD88 L265P and CXCR4 WHIM genotyping.

An allele-specific polymerase-chain-reaction (PCR) assay will be used to detect $MYD88^{L265P}$ mutations. $CXCR4^{WHIM}$ mutation status will be determined by means of Sanger sequencing, and allele-specific PCR will be used to detect $CXCR4^{S338X}$ C→G and C→A mutations in CD19-selected bone marrow cells (Xu et al, 2013; Hunter et al,2014; Treon et al, 2014). For PCR assays two large lavender tops of bone marrow aspirate will be collected at the time of the screening bone marrow biopsy. In the event there is insufficient material for performance of assays, two lavender tops will be collected on subsequent bone marrow aspirations to perform these assays.

10. STUDY CALENDAR

	Screening*	**Treatment Phase[7]** 48- four week cycles (4 years)		**Off Treatment Assessment**	**Follow-Up Phase**
	≤ 30days from study entry	Cycles 1*, 2 (4 weeks ± 5 days)	Cycles 3, 6, 9, etc. until 48 four week cycles completed (12 weeks± 2 weeks)	Within 4 weeks of completion of entire treatment plan or removal from study ± 2 weeks	Post Treatment; Every 24 weeks ± 2 weeks for 2 years or until next therapy[9]
Physical exams[1], vital signs, weight	X	X	X	X	
Medical History	X				
ECOG performance status (see Appendix A)	X				
CT of the chest & abdomen / pelvis[2]	X		X[2]		X (if applicable)
Bone marrow biopsy and aspiration[3]	X		X[3]		X (if applicable)
Quantitative serum IgM, IgG, IgA, free light chain assays	X	X	X	X	X
Serum immuno-electropheresis	X	X	X	X	X (if applicable)
Complete Blood Count plus differential[1,4]	X	X	X	X	X
Coagulation profile: PT, PTT, PT-INR[5]	X				
Chemistry/ Comprehensive Metabolic Panel including: Electrolytes, Renal (BUN, Creatinine) and Hepatic function testing [ALT (SGPT), AST (SGOT), Alk phos, total Bilirubin, albumin, and total protein]	X	X	X	X	X
Peripheral blood flow cytometry	X	X	X[8]		
Pregnancy Test[6]	X				
Magnesium	X	X			
Beta-2 microglobulin test	X				
Review patient diary		X	X		
Adverse event monitoring (see section 6)		X	X	X	

* Labs, Physical exam, vital signs, and weight do not need to be repeated if Cycle 1, Day 1 is within 28 days of Screening. Cycle 1, Day 1 labs, if drawn, do not need to re-confirm eligibility prior to administering first dose.

[1]More frequent visits may be required at the discretion of the treating physician.

[2]**If CT scans of the chest, abdomen and pelvis have been collected and done within 90 days of screening they will not be required at the screening visit.** Scans will be **repeated at cycle 6, 12, 24, 36, and 48, for participants with extramedullary disease at baseline defined as adenopathy >1.5 cm in any axis, and splenomegaly >15 cm in the craniocaudal axis.** Scans will also be repeated to confirm a complete response if the participant has no detectable monoclonal protein and had extramedullary disease at baseline, and at the discretion of the investigator.

[3]Bone marrow biopsy and aspirations are **required at baseline, and at cycle 6, 12, 24, 36, and 48, or at time of progression.** Bone marrow biopsy and aspiration may also be done at the investigator's discretion, and at any time to confirm a complete response if the participant has no detectable monoclonal protein. Bone marrow aspirates will be used for tumor cell sorting, and for whole genome and transcriptome Four 10 ml heparinized tubes of bone marrow aspirate and 2 Lavender tops of bone marrow aspirate for Dr. Treon's Laboratory for genome studies will be collected for genomic studies described in section 9.1.

[4]For patients who demonstrate therapy related hematological toxicity, more frequent CBC evaluations are strongly recommended.

[5]Coagulation profile. Prothrombin time (PT) will be performed at screening and repeated as clinically indicated. PT will be reported as well as the international normalized ratio (INR).

[6]For women of child-bearing potential only, a serum pregnancy test will be required at screening.

[7]Please refer to Section 6 for Dose Modifications.

[8]Cycles 3, and 6 only.

[9]More frequent visits/unscheduled visits may be required/considered at the discretion of the treating physician.

11. MEASUREMENT OF EFFECT

For the purposes of this study, participants should be re-evaluated every 4 weeks ± 5 days for cycles 1, 2, and 3 and thereafter every 12 weeks ± 2 weeks for the remaining cycles for a total of 48 cycles, and within 4 weeks ± 2 weeks from when a participant is removed from trial or when treatment is completed. Post-treatment, patients will continue to be followed-up every 24 weeks ± 2 weeks for 2 years. Participants will be assessed for efficacy by consensus panel criteria according to section 11.1.2 below adopted from the Third International Workshop on WM (Anderson et al, 2012).

11.1 Definitions

Evaluable for toxicity: All participants who have received at least one dose of study drug will be evaluable for toxicity.

Evaluable for objective response: Applicable to those participants who have received at least one cycle of therapy, and have had their disease re-evaluated. These participants will have their response classified according to the definitions stated below.

11.1.1 Response Criteria

Complete Response (CR): A complete response (CR) is defined as having resolution of WM related symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. A complete response requires reconfirmation demonstrating normal serum IgM levels, and absence of IgM paraprotein by immunofixation by a measurement repeated at least 2 weeks later.

Very Good Partial Response (VGPR): is defined as $\geq$ 90% reduction in serum IgM levels, or normalization of serum IgM levels.

Partial Response (PR): Partial response (PR) is defined as achieving a $\geq$ 50% reduction in serum IgM levels.

Minor Response (MR): A minor response (MR) is defined 25-49% reduction in serum IgM levels.

Stable Disease (SD): Stable disease is defined as having < 25% change in serum IgM levels, in the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM.

Progressive Disease (PD): Progressive disease (PD) is defined as occurring when a greater than 25% increase in serum IgM level occurs (with an absolute increase of at least 500 mg/dL) from the lowest attained response value, or progression of clinically significant disease related symptom(s). Reconfirmation of the initial IgM increase is required when IgM is the sole criterion for progressive disease confirmation. Death from any cause for WM will also be considered a progression event. For participants on active therapy who are on a drug hold for > 3 days, serum IgM levels will be considered unevaluable for response assessment. Patient must be on study drug for >2 consecutive weeks to be considered eligible for serum IgM response assessment. An increase of 1 cm in any axis for adenopathy, or 2 cm in the craniocaudal axis of the spleen will be considered evidence of progression of extramedullary disease. Development of Bing Neel syndrome, or other extramedullary disease manifestations, as well as disease transformation will be considered as progressive events.

Non-response (NR): Persistant signs or symptoms of WM disease that prompted therapy despite at least three months of continuous treatment on ibrutinib.

11.1.2 Confirmation of Response

Confirmation of response will be done by bone marrow biopsy and CT scans at cycles 6, 12, 24, 36, and 48 .

11.1.3 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression or death. Median PFS, as well as 2-year and 4-year landmark PFS analyses will be performed.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 **Method**

The QACT will collect, manage, and perform quality checks on the data for this study.

12.1.2 **Responsibility for Data Submission**

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

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.

13. STATISTICAL CONSIDERATIONS

This is single arm, open label, Phase II, single center study designed to evaluate the safety and efficacy of ibrutinib in previously untreated WM patients. Treatment will be administered in 4-week cycles, and participants will receive treatment for up to 48 cycles. Treatment will be comprised of ibrutinib at 420 mg per day by oral administration.

13.1 Study Design/Endpoints

The primary endpoint of this study is to assess the Major Response Rate (PR or better). Overall response rates (MR or better), and Very Good Partial Response/Complete Response (VGPR/CR) of ibrutinib in previously untreated, symptomatic WM patients will also be evaluated. The analysis for the primary endpoint, Major response rate (PR or better), will be based on the evaluable population. The evaluable population will be defined as all enrolled subjects who have received at least 1 cycle of study drug, and who have had at least 1 post-baseline disease assessment. The null hypothesis is that the major response rate (PR or better) will be 40% or lower. The major response rate and its exact 95% confidence intervals (CI) will be calculated and the null hypothesis will be rejected if the lower bound of the 95% confidence interval exceeds 40%. The analysis for overall response (MR or better) will be similarly evaluated. In addition, the number and percent of subjects by best overall response (CR, VGPR, PR, MR, SD, or PD) will be summarized.

13.2 Sample Size, Accrual Rate and Study Duration

A total of up to 33 participants will be enrolled. With the enrollment of 30 evaluable participants, based on the assumption that the Major Response Rate for ibrutinib is 70%, the study will have slightly greater than 90% power to declare that the lower bound of the two-sided 95% CI for Major Response Rate will exceed 40%. A Major Response Rate of 18/30 or higher will be required to declare the trial as having met its primary endpoint. In the study of previously treated, relapsed/refractory WM patients (n=63), the observed Major Response Rate was 73.0% (95% CI,

62.04 to 83.96). It is expected that the Major Response Rate in untreated WM would be similar or better than the Major Response Rate in previously treated patients.

13.3 Stratification Factors

No stratification factors will be applied to any analysis.

13.4 Interim Monitoring Plan

See section 13.2.

13.5 Analysis of Primary Endpoints

See section 13.1

13.6 Analysis of Secondary Endpoints

The secondary endpoints include:

- The safety and tolerability of ibrutinib in previously untreated, symptomatic WM patients.
- Duration of response (DOR), time to response (TTR), progression-free survival (PFS) and overall survival (OS)
- To identify genomic variants associated with ibrutinib response, response duration and acquired resistance, including evolution of subclonal variants present at baseline.

Adverse events for events deemed grade 1 or higher shall be captured for those toxicities that are deemed by the investigators to be at least possibly related to study drug based on attributions denoted in the medical record. The investigators shall review patient diaries, and only those toxicities deemed at least possibly related to study drug shall be recorded in the medical record.

PFS and OS analysis to will be performed using the Kaplan-Meier methodology, median and associated confidence intervals will be presented, and participants will be censored at the time of last relevant assessment if they have not demonstrated the event of interest by the end of the study. A 2-year and 4-year landmark analysis will be also performed for PFS and OS. Duration of response will be similarly evaluated using the Kaplan-Meier methodology. Time to response will

be evaluated as continues variable and summarized (median, range) for participants who achieved response. An update of these endpoints will also be provided at the end of the study, which is defined as 4 weeks after completion of follow-up for the last participant.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

Evaluation of toxicity. All participants who receive at least one dose of any test material during the study will be included in the safety analysis.

13.7.2 Evaluation of the Primary Efficacy Endpoint

Evaluation of response. All participants who have received at least one cycle of therapy, and have had at least one assessment for treatment response will be considered evaluable for purposes of response assessment, even if these patients have encountered major protocol treatment deviations, or were later deemed to have been ineligible for this study. Each participant should be assigned a response category based on the response criteria in Section 11.1.1

14. PUBLICATION PLAN

Any formal presentation or publication of data from this trial may be published after review and comment by Pharmacyclics LLC prior to any outside submission. Pharmacyclics LLC must receive copies of any intended communication in advance of publication (at least 2 weeks for presentational materials and abstracts, and 4 weeks for manuscripts). These requirements acknowledge PharmacyclicsLLC's responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. The principal investigator shall have the final authority to determine the scope and content of resulting publications, provided such authority shall be exercised with reasonable regard for proprietary interests and not permit disclosure of confidential or proprietary information that belongs to Pharmacyclics LLC. Anticipated analysis and presentations or publications are listed below:

First interim analysis – when all patients completed 6 months of treatment.
First Interim analysis presentation –ASCO or ASH 2016.

Second interim analysis – when all patients would have completed 2 years of study.
Second interim analysis presentation – ASH 2017.
Completion of study report (CSR) – by September 1, 2019.
Publication date – shortly after second interim analysis (preliminary report). Final report at time of CSR.

Protocol Amendments

Per the IST Agreement, any amendments to the Protocol or Informed Consent Form 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.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B. 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.
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