A Phase 2 Study of the Effect of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib on Disease Response in Patients with High Risk Smoldering Multiple Myeloma

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# IST PROTOCOL

**TITLE:** A Phase 2 Study of the Effect of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib on Disease Response in Patients with High Risk Smoldering Multiple Myeloma

**PROTOCOL NUMBER:** **20053**

**STUDY DRUG:** Ibrutinib (PCI-32765)

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**DATE FINAL:** 17 July 2017

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## SYNOPSIS

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| **Study Title:** | A Phase 2 Study of the Effect of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib on Disease Response in Patients with High Risk Smoldering Multiple Myeloma |
| **Protocol Number:** | *20053* |
| **Study Phase:** | 2 |
| **Study Duration:** | Two years |
| **Investigational Product and Reference Therapy:** | Ibrutinib (PCI-32765) 140 mg hard gelatin capsules, for oral (PO) administration. |
| **Objectives:** | **Primary Objective:**<br>To evaluate the proportion of patients with high risk smoldering multiple myeloma who do not progress to symptomatic myeloma as defined by the IMWG after 12 cycles (each 28 days) of ibrutinib therapy.<br><br>**Secondary Objectives**:<br>1. Overall response rate, defined as partial response or better per IMWG criteria<br>2. Changes in bone density and qCT, particularly in patients with osteopenia (defined as T-score on bone densitometry testing (DEXA) of -1 to -2.5).<br>3. Changes in PET-MRI, particularly in patients with osteopenia<br>4. Changes in bone related biomarkers, particularly in patients with osteopenia:<br>a. Serum: interleukin-6 (IL-6), stromal cell-derived factor-1 (SDF-1), receptor activator of nuclear-factor kappa B ligand (RANKL), macrophage inflammatory protein-1α (MIP-1α), Dickkopf-1 (DKK-1), C-terminal telopeptide (CTX)<br>b. Urine: N-terminal telopeptide (NTx)<br>5. Genomic and immunologic correlatives in a separate companion study |
| **Study Design:** | This is a phase 2, open-label, single center, prospective pilot study designed to assess the efficacy of ibrutinib in subjects with high risk smoldering multiple myeloma.<br><br>All enrolled subjects will be treated with ibrutinib 560 mg (4 capsules, each containing 140 mg) taken PO daily for 12 cycles (28 days each). If a subject demonstrates benefit from ibrutinib, therapy may be extended beyond 12 cycles to a maximum of 2 years. Subjects who progress and meet criteria for symptomatic multiple myeloma will be withdrawn from study.<br><br>An initial cohort of 15 subjects will be accrued. If 4 or more patients progress to symptomatic myeloma in one year, then the study will be |

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| | reviewed with the FDA to determine whether to employ a higher dose of ibrutinib, or to stop for futility. Otherwise, 21 additional patients will be accrued for a total sample size of 36. |
| **Population:** | Patients with high risk smoldering multiple myeloma. |
| **Centers:** | Single |
| **Inclusion Criteria:**<br><br>*Refer to* Section 4.0 *for the complete and detailed list of inclusion/exclusion criteria.* | *Disease Related*<br><br>The following patients will be considered for enrollment:<br>• 36 evaluable patients with high risk smoldering multiple myeloma, defined as having bone marrow plasma cells between 10% and 60%, with one of the following:<br>o High paraprotein burden: Serum M-protein ≥ 3 g/dL [except IgA ≥ 2 g/dL] or urine M-protein > 500 mg per 24 hours<br>o Moderate paraprotein burden: [(serum m protein < 3 g/dl but > 1 g/dl) or (urine m-protein > 200 mg/24h)] AND serum free light chain ratio < 0.126 or > 8<br>o involved to uninvolved free light chain ratio of > 100<br>o abnormal plasma cell phenotype ≥ 95% and immunoparesis (defined by a reduction below the lower limit of normal in 1 or 2 of the uninvolved immunoglobulins)<br>o evolving type of smoldering MM defined as<br>▪ :⩾10% Increase in serum M-protein and/or involved immunoglobulin level within the first 6 months of diagnosis (only if baseline M-protein was ⩾3 g/dl)<br>*and/or*<br>▪ ⩾25% increase in serum M-protein and/or involved immunoglobulin level within the first 12 months of diagnosis (for any level of M-protein) *plus minimum increase of* 0.5 g/dl in M-protein or 500 mg/dl in immunoglobulin or both<br>o presence of translocation (4;14) or deletion 17 p<br>• Measurable disease, defined as M-protein ≥ 1 g/dL OR Bence-Jones protein (BJP) > 200 mg/24 hr OR involved free light chain > 100 mg/dL<br>• Diagnosed with smoldering myeloma within the last 4 years<br><br>*Laboratory*<br><br>• Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening and:<br>o Absolute neutrophil count > 750 cells/$mm^3$ (0.75 x $10^9$/L)<br>o Platelet count > 75,000 cells/$mm^3$ (75 x $10^9$/L)<br>• Adequate hepatic and renal function defined as:<br>o Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN)<br>o Estimated creatinine clearance ≥ 30 mL/min (Cockcroft-Gault)<br>o Bilirubin ≤ 1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, in which case the total |

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| | bilirubin should be < 3 x ULN)<br>• PT/INR < 1.5 x ULN and PTT (aPTT) < 1.5 x ULN<br><br>*Demographics*<br>• Men and women ≥ 18 years of age<br>• Eastern Cooperative Oncology Group (ECOG) performance status of < 2 |
| **Exclusion Criteria:** | *Disease-Related*<br>• No end organ damage attributable to a plasma cell disorder, defined as having ANY of the following:<br>o Hypercalcemia: Serum calcium > 1 mg/dL above the upper limit of normal or > 11 mg/dL<br>o Renal insufficiency: Serum creatinine > 2 mg/dL or creatinine clearance < 30 mL per min<br>o Anemia: Hemoglobin > 2 g/dL below the lower limit of normal or hemoglobin < 10 g/dL<br>o Bone lesions: One or more lytic lesions on skeletal radiography, CT, MRI, PET-CT, or PET-MRI<br>• Bone marrow plasma cells < 10% or > 60%<br>• Has received prior anti-myeloma therapy of any type<br>• Has received prior bisphosphonate therapy<br>• Has received an investigational drug, investigational vaccine, or has used an investigational medical device within 4 weeks or 4 half-lives, whichever is longer, before Cycle 1, Day 1 of study therapy<br>• Osteoporosis, defined as having a T-score on DEXA of ≤ -2.5<br><br>*Concurrent Conditions*<br>• History of other malignancies, except:<br>o Malignancy treated with curative intent with no known active disease for ≥ 3 years before the first dose of study medication and felt to be at low risk for recurrence by treating physician<br>o Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease<br>o Adequately treated carcinoma in situ without evidence of disease<br>• Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc.), or administration of corticosteroid medication EITHER for > 14 days OR at dosages of > 20 mg/day of prednisone or equivalent<br>• Vaccinated with a live, attenuated vaccine within 4 weeks of first study treatment |

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| | • Recent or active infection requiring systemic treatment within 14 days of the first study treatment<br>• Known bleeding disorders (eg, von Willebrand's disease, hemophilia)<br>• Concomitant use of warfarin or other vitamin K antagonists within 7 days of treatment initiation<br>• Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor or inducer (see Appendix 3)<br>• History of stroke or intracranial hemorrhage within 6 months prior to enrollment<br>• Known history of human immunodeficiency virus (HIV), or active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. 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.<br>• Major surgery within 4 weeks of first study treatment<br>• Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to start of first study treatment<br>• Currently active, clinically significant hepatic impairment (≥ mild hepatic impairment according to the Child Pugh classification (Appendix 5)<br>• Unable to swallow capsules, malabsorption syndrome, prior resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, partial or complete bowel obstruction, or any other disease significantly affecting gastrointestinal function<br>• Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigators' opinion, could compromise the subject's safety or put the study outcomes at undue risk |
| **Study Treatment:** | Ibrutinib 560 mg (4 hard gelatin capsules, each containing 140 mg) for oral (PO) administration. |
| **Concomitant Therapy:** | *Permitted Concomitant Therapy*<br>Standard supportive agents (eg, for nausea, diarrhea) are permitted as clinically indicated. Short courses (< 14 days) of corticosteroids at dosages equivalent to prednisone ≤ 20 mg per day for treatment of non-cancer-related medical reasons are permitted<br><br>*Prohibited Concomitant Therapy*<br>Myeloma-targeted therapy including immunomodulatory agents (eg, lenalidomide), proteasome inhibitors (eg, bortezomib), histone deacetylase inhibitors, or bisphosphonates. Any use of corticosteroids EITHER for > 14 days OR at dosages > 20 mg/day of prednisone or equivalent is prohibited. |

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| | Strong CYP3A4 inhibitors. Any other chemotherapy, anticancer immunotherapy, radiotherapy, or other experimental therapies are prohibited.<br><br>Refer to Appendix 2 for guidance on drugs that are CYP P450 inhibitors. Refer to Section 6.2.4 for guidance on concomitant use of anticoagulants. |
| **Safety Plan:** | Utilizing a 30% toxicity rate (based upon all event terms of Grade 3 or greater), sequential boundaries will be used to monitor all enrolled subjects. The accrual will be halted if excessive toxicities are seen. See table in Section 10.5 for boundaries.<br><br>Data and safety will be monitored by an internal Data and Safety Monitoring Board (DSMB) chaired by the PI. Other members of the committee will include co-investigators, the myeloma research program manager, and clinical research coordinators. All of these individuals have experience in clinical care as well as clinical research and monitoring of subjects with multiple myeloma. A statistician will also serve as a member of the committee.<br><br>*Expected* events in a population of patients with smoldering multiple myeloma include progression to multiple myeloma (as evidenced by hypercalcemia, renal insufficiency, anemia, lytic bone lesions, and ≥ 60% bone marrow plasma cells), infections, and venous thromboembolism. These events will be monitored for frequency and severity. If the investigators become aware that an otherwise expected adverse event has increased in severity or frequency, these will be promptly reported to the Tisch Cancer Institute (TCI) Data and Safety Monitoring Committee (DSMC), the IRB, and Pharmacyclics as an unexpected event. All deaths and any unanticipated serious adverse events will be reported to these three groups as well as to the FDA. The study will be stopped until the event has been fully evaluated and discussed with the FDA.<br><br>The myeloma research program manager will log and track all adverse events (graded by NCI CTC criteria), subject enrollment, and protocol compliance. These findings will be systematically reviewed by the DSMB after the first three patients have completed 3 months of study treatment and thereafter every four months. A written report of the DSMB's findings will be generated. This report will be sent to the TCI DSMC. If the DSMB determines that due to safety or concern about lack of efficacy the study must be halted or the protocol modified, the TCI DSMC, IRB, and Pharmacyclics will be promptly notified and provided a copy of the written report. |
| **Statistical Methods and Data Analysis:** | All efficacy analyses will be performed using the intent-to-treat (ITT) population.<br><br>**<u>Primary efficacy analysis:</u>**<br>Proportion of patients who do not progress to symptomatic myeloma by |

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| | IMWG criteria (except serum free light chain ratio – subjects who start at or develop a serum free light chain ratio ≥100 will be permitted to be on study) at 1 year amongst subjects who have completed at least 1 cycle.<br><br>**Secondary efficacy analysis:**<br>1. Overall response rate, defined as partial response or better by IMWG criteria<br>2. In subjects with osteopenia, improvements in bone density by DEXA and qCT with fine element analysis in all subjects<br>3. Changes in PET-MRI<br>4. Changes in bone related biomarkers:<br>a. Serum: IL-6, SDF-1, RANKL, MIP-1α, DKK-1, CTX<br>b. Urine: NTx<br>5. Genomic and immunologic correlatives in a separate companion study |
| **Sample Size Determination** | Null hypothesis: Approximately 25% of high risk SMM patients are expected to progress to symptomatic MM at 1 year.<br><br>Alternative hypothesis: Given that disease stabilization on ibrutinib monotherapy was 30% in relapsed or relapsed/refractory MM patients with a median of 4 prior therapies (range 2-14), we hypothesize that for a treatment naïve high risk SMM population, ibrutinib monotherapy will stabilize disease progression in most patients and only 10% of patients will progress at 1 year.<br><br>Using a Simon's two-stage design, we plan to enroll 15 patients in the first stage. If 4 or more progress, the study will be stopped for futility. If 12 or more responses are observed, an additional 21 patients will be accrued, for a total sample size of 36. The null hypothesis will be rejected if 30 or more responses are observed in 36 patients. This design yields a type I error rate of 15% and power of 90% when the true response rate is 90%. |

## ABBREVIATIONS

| | |
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| BCR | B-cell receptor |
| BJP | Bence Jones protein |
| BM | bone marrow |
| BTK | Bruton's tyrosine kinase |
| CLL | chronic lymphocytic leukemia |
| CR | complete response |
| CRF | case report form (paper or electronic as appropriate for this study) |
| CTX | C-terminal telopeptide |
| DCF | data clarification form |
| DEXA | bone densitometry |
| DKK-1 | Dickkopf-1 |
| DMC | Data Monitoring Committee |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders (4th edition) |
| ECG | Electrocardiogram |
| eDC | electronic data capture |
| FDA | Food and Drug Administration |
| FEA | fine element analysis |
| FISH | fluorescent in situ hybridization |
| GCP | Good Clinical Practice |
| GEP | gene expression profile |
| HBsAg | hepatitis B surface antigen |
| HIV | human immunodeficiency virus |
| IAC | Interim Analysis Committee |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IL-6 | interleukin-6 |
| IMWG | International Myeloma Working Group |
| IRB | Institutional Review Board |
| ITK | interleukin-2-inducible kinase |
| IVRS | interactive voice response system |
| IWRS | interactive web response system |
| LC-MS/MS | liquid chromatography/mass spectrometry/mass spectrometry |
| MCL | mantle cell lymphoma |
| MedDRA | Medical Dictionary for Regulatory Activities |

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| MIP-1α | macrophage inflammatory protein 1α |
| MM | multiple myeloma |
| MR | minimal response |
| MRU | medical resource utilization |
| NTx | N-terminal telopeptide |
| OC | osteoclast |
| PC | plasma cells |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PQC | Product Quality Complaint |
| PR | partial response |
| PRO | patient-reported outcome(s) |
| QCT | quantitative computer tomography scan |
| QTc | corrected QT interval |
| RANKL | Receptor activator of nuclear factor kappa-B ligand |
| sCR | stringent complete response |
| SD | stable disease |
| SDF-1 | stromal cell-derived factor-1 |
| SLL | small lymphocytic lymphoma |
| SMM | smoldering multiple myeloma |
| USP | United States Pharmacopeia |
| VGPR | very good partial remission |

# 1. BACKGROUND

## 1.1. Disease

Myeloma cells are highly dependent upon the bone marrow microenvironment for their growth and survival. This microenvironment includes cytokines and chemokines (eg, interleukin-6 (IL-6), vascular endothelial growth factor, basic fibroblast growth factor-2), macromolecules in the extracellular matrix, and supportive (stromal) cells. Adhesion of myeloma cells to bone marrow (BM) stromal cells triggers secretion of various cytokines and chemokines which augment myeloma cell growth and survival and confers drug resistance. Additionally, myeloma cells stimulate osteoclastogenesis by secretion of various factors, including receptor activator of nuclear factor κB ligand (RANKL), IL-6, and macrophage inhibitory protein-1α (MIP-1α). Collectively, these interactions contribute to a favorable microenvironment for myeloma cell adhesion and proliferation.[1-6]

Smoldering multiple myeloma (SMM) is an asymptomatic plasma cell neoplasm that is a precursor state of symptomatic multiple myeloma (MM). It is defined by the presence of a serum M-protein ≥ 3 mg/dL or urinary M-protein ≥ 500 mg per 24 hours, and by the absence of end-organ damage attributable to plasma cells, myeloma defining events, or amyloidosis.[7] SMM is associated with a high risk of progression (10% per year, or 73% at 15 years) to MM. A high risk subset of SMM defined by Mayo Clinic criteria as having bone marrow plasma cells 10-60% and serum M-protein ≥ 3 g/dL or urine M-protein > 500 mg per 24 hours and serum free light chain ratio < 0.126 or > 8 has an even more rapid course, with approximately 50% of patients progressing at 2 years and 25% of patients progressing at 1 year.[8,9] Given that MM is an incurable malignancy with a high morbidity burden, effective approaches to decreasing or delaying its development are much needed.

Recently, an involved to uninvolved sFLC ratio of ≥ 100 was classified as a myeloma defining event even in the absence of so called CRAB symptoms (hypercalcemia, renal insufficiency, anemia, or lytic bone disease). The current evidence for use of the comes from 3 studies, 2 of which have been published.[10-12] Two of these studies were relatively small, with sample sizes of 96 and 126, and all were retrospective. Two studies were single institution studies, which are subject to referral bias, and the third does not specify where patients were recruited from. Another recently published study offers conflicting results to the previous 3. In this study, 321 patients in the Danish Multiple Myeloma Registry between 2005-2014 were evaluated for factors predicting progression. 23 of 321 patients with SMM had a sFLC of > 100. After 2 years of follow-up, only 30% of patients with sFLC > 100 had progressed to myeloma.[13]

**1.1.1. None of the studies cited above consider or account for lead time bias, wherein patients are stratified by time since initial detection of plasma cell burden. Most importantly, there are no prospective trials which demonstrate that early treatment of patients with sFLC ≥ 100 will improve outcomes relative to the current standard of care. Given the lack of definitive evidence, there are inadequate data to support the treatment of individuals for SMM solely on the basis of a sFLC ≥ 100 alone and therefore this population merits inclusion in prospective clinical trials such as the present study.**

### 1.1.2. Current Treatment Options

The current standard of care for patients with SMM is observation.[14] However, there is significant interest in examining early intervention, particularly for patients who have high risk SMM. In 2013, Mateos et al reported that the use of lenalidomide and dexamethasone for 9 cycles followed by lenalidomide maintenance for 24 months was associated with a prolonged median time to progression and higher 3-year survival rate.[15] In this study, 40% of the patients on the placebo arm who progressed to MM did so by virtue of bone disease, suggesting that delay or prevention of the onset of bone disease may be a valuable therapeutic target.[16] Overall, this study provided proof of concept that early intervention in high risk SMM is feasible and might impact disease outcome.

Traditionally, SMM has not been an ideal stage for therapy because patients do not have symptoms, and because the therapies for multiple myeloma have considerable toxicities. Such therapies initially consisted of chemotherapy, many of which are alkylating agents, and steroids. These agents have significant immediate toxicities as well as potential long term toxicity to the bone marrow. The subsequent introduction of immunomodulatory drugs such as thalidomide, lenalidomide, and pomalidomide, and proteasome inhibitors such as bortezomib and carfilzomib, has broadened the armamentarium against myeloma. However, these agents also have significant toxicities, raising concern about their use in SMM. There is an urgent need for therapies which are well-tolerated and which have disease-modifying properties for SMM patients.[17,18]

### 1.1.3. Role of BTK in Disease/Histology

Bruton's tyrosine kinase (BTK) is a central mediator of B-cell receptor (BCR) signaling. B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the BCR, which is activated by binding to antigen. Antigen binding induces receptor aggregation and clustering and activation of multiple tyrosine kinases including BTK, which in turn activate further downstream signaling pathways.[19]

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development.[20] Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

In normal plasma cells, BTK is markedly down-regulated. However, it is highly expressed in the malignant cells from many myeloma patients and some cell lines. Chauhan et al, showed that BTK mRNA expression was 2.3-fold increased in 6 MM patient specimens compared to normal human marrow precursors.[21] Tai et al, noted increased expression in 84% of primary myeloma samples and among some cell lines, especially ANBL-6 and INA-6, both of which are IL-6 dependent.[22] Bam et al, reported expression particularly among cases within the MF gene expression profile (GEP) grouping, and also commonly in cases within the DC-1, DC-2, HY, and LB subgroups.[23-25]

## 1.2. Study Rationale

### 1.2.1. Mechanistic/Pre-clinical

We hypothesize that ibrutinib has important clinical activity in MM/SMM by: (1) inhibitory effects upon osteoclast (OC) function and development resulting in less bone destruction and improved bone density, (2) modulation of microenvironmental interactions important for MM cell adherence and growth, and (3) reduction of MM repopulating cell growth.

Recent observations have shown that BTK is important in OC function and development. Mice with X-linked immunodeficiency have monocytic OC precursor cells that are defective in multinucleate OC formation in response to RANKL.[26] BTK/TEC knockout (KO) mice (but not BTK KO mice) have osteopetrotic bones due to defective osteoclast formation.[27] Patients with X-linked agammaglobulinemia have a similar defect in OC formation *in vitro*. This is masked *in vivo*, thought to be due to higher than normal levels of regulatory cytokines.[28] Ibrutinib has been found to inhibit *in vitro* the production of human OC from progenitors, as well as cytokine and chemokine secretion[29]. Erosion of human bone chips by myeloma xenografts in mice with severe combined immunodeficiency was inhibited by ibrutinib, as was progression of the tumor itself.[22]

Ibrutinib has also been shown to inhibit stromal adherence of plasma cells. Multiple myeloma cells, particularly ones with the MF gene expression profile (GEP), are known to be particularly dependent upon microenvironmental interactions and integrin β7-based adherence to the bone marrow stroma.[30] Ibrutinib has been shown to decrease SDF-1 induced migration of MM cells, and decrease MIP-1α (a chemokine which has been shown to enhance adhesion of MM and bone marrow stromal cells) expression in MM cells.[22]

The putative myeloma stem cell or cancer regenerating cell as identified by Matsui was found to be enriched in the $CD138_{neg}$ subfraction of both MM patient samples and cell lines.[31] This functionally defined cell was found to have phenotypic features generally consistent with a memory B cell phenotype, including a BCR component and associated marker proteins, and small cell lymphoid morphology. Two groups have independently reported increased BTK expression in cell subfractions ($CD138_{neg}$ or $CXCR4^{+}$) and expect them to be enriched for this colony forming population, compared to the bulk population of MM cells.[22,23] Consistent with this observation, Matsui found ibrutinib to be inhibitory to *in vitro* colony formation by $CD138_{neg}$

cells (but not growth of CD138+ cells in bulk culture) from 5/5 patient samples tested at concentrations as low as 10 nM.[32] A selective effect of ibrutinib on the self-renewing subpopulation would further explain the difficulty of documenting inhibition of short-term cultures of predominantly CD138+ non-fractionated cells. Such a selective effect could be advantageous for clinical use in SMM, as putative stem cells tend to be resistant to conventional antineoplastic agents.

### 1.2.2. Clinical

In an open-label, phase 2, dose escalation study utilizing ibrutinib as single agent or in combination with dexamethasone in patients who were heavily pre-treated (median prior therapies = 4), anti-tumor activity was noted. The group of patients (with n = 20) receiving ibrutinib 840 mg daily with dexamethasone 40 mg weekly appeared to have the most benefit, with 1 attaining a PR, 4 MRs, and 6 SD. Other groups receiving ibrutinib as single agent, or lower doses of ibrutinib appeared to have benefit as well, with significant numbers of patients attaining SD or better. In this study of heavily pre-treated patients, diarrhea (51%), fatigue (41%), nausea (35%), dizziness (25%), and muscle spasms (23%) were the most common Grade 3 or higher adverse events. Dose modifications occurred in 22% of patients (out of a total of 69 as of May 2014), with 6 discontinuing due to an adverse event. Correlative studies are ongoing to identify markers which reflect biologic activity of ibrutinib.[33]

Another study (NCT 01962792) is currently examining the combination of ibrutinib with carfilzomib in the relapsed or relapsed and refractory setting. Phase 1 of this study is a dose escalation, and phase 2b is a randomized, double-blind, placebo-controlled study to evaluate the efficacy of this combination in terms of overall response rate and duration of response. Preliminary results reveal an overall response rate of 58% in 36 evaluable patients. In the best responding cohort of patients, who received ibrutinib 840 mg daily and carfilzomib 20 then escalated to 36 mg/m$^2$, the overall response rate was 65%, with 3 VGPRs and 1 sCR.[34]

## 1.3. Investigational Product Name and Description

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of BTK. Inhibition of BTK blocks downstream BCR signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. Ibrutinib (IMBRUVICA®) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of: 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) in patients who have received at least one prior therapy, 3) CLL in patients with 17p deletion, and 4) Waldenström's macroglobulinemia. Ibrutinib is currently under investigation in various other indications.

Data from study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post-dose at dose levels ≥ 2.5 mg/kg. In study PCYC-

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

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

## 1.4. Summary of Nonclinical Data

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

### 1.4.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor ofBTK.[35] In vitro, ibrutinib is a potent inhibitor of BTK activity ($IC_{50}$ = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation ($IC_{50}$ = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression.[36]

Ibrutinib arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines *in vitro* and inhibited tumor growth *in vivo* in xenograft models.[36] Ibrutinib also inhibited adhesion and migration of MCL cells in co-culture and reduced tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression.[37]

In multiple myeloma, ibrutinib has been found to be cytotoxic via an inhibitory effect on the nuclear factor-kB (NF-kB) pathway. By blocking the phosphorylation of serine-536 of the p65 subunit of NF-kB, ibrutinib prevents the nuclear translocation of NF-kB, resulting in down-regulation of the anti-apoptotic proteins Bcl-xL, FLIP(L) and survivin.[38]

### 1.4.2. Toxicology

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

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human

correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

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

#### 1.4.2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

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

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

### 1.5. Summary of Clinical Data

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

#### 1.5.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration ($T_{max}$) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

## 1.6. Summary of Clinical Safety

### 1.6.1. Monotherapy Studies

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

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

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

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

### 1.6.2. Risks

#### 1.6.2.1. Bleeding-related events

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

#### 1.6.2.2. Atrial fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.3.1.4).

#### 1.6.2.3. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.3.1.4).

#### 1.6.2.4. 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.

#### 1.6.2.5. Non-melanoma Skin Cancer

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

#### 1.6.2.6. 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.

#### 1.6.2.7. 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

#### 1.6.2.8. 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 5.3.1.4).

#### 1.6.2.9. Cytopenias

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

#### 1.6.2.10. 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 5.3.1.5.

**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.



## 2. STUDY OBJECTIVE

### 2.1. Primary Objective

To evaluate the proportion of patients with high risk smoldering myeloma who have not progressed to symptomatic myeloma by IMWG criteria (except sFLC – a sFLC ratio of ≥ 100 will not disqualify subjects from enrolling or continuing in the study) after 12 cycles (each 28 days) of ibrutinib therapy.

### 2.2. Secondary Objectives

1. Overall response rate, defined as achieving partial response or better per IMWG criteria (see Appendix 3)

2. Changes in bone density and qCT after 12 cycles of ibrutinib therapy, particularly in subjects with osteopenia.

3. Changes in PET-MRI findings after 12 cycles of ibrutinib therapy, particularly in subjects with osteopenia.

4. Changes in bone related biomarkers in urine and serum after 12 cycles of ibrutinib therapy, particularly in subjects with osteopenia.

5. A separate but companion correlative study will examine possible baseline predictors of response as well as alterations associated with ibrutinib therapy at the genomic and immunologic levels.



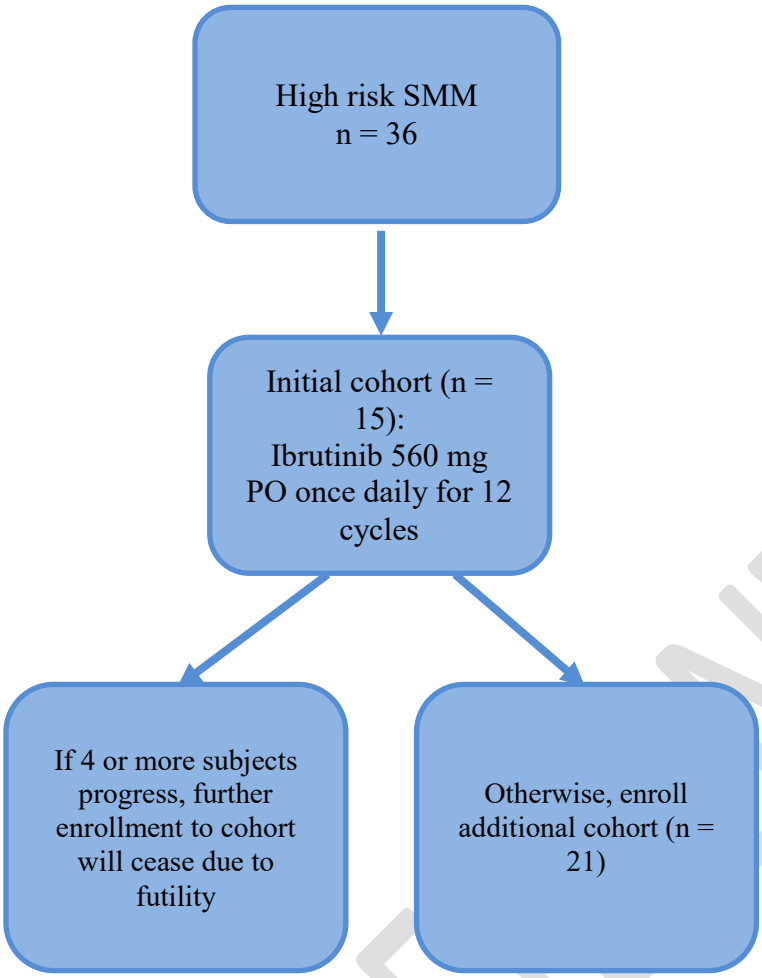
# 3. STUDY DESIGN

## 3.1. Overview of Study Design

This is a phase 2, open-label, nonrandomized, single center study designed to assess the efficacy of ibrutinib in patients with high risk SMM.

Up to 36 patients with high risk SMM will be enrolled. All subjects will take ibrutinib at a dose of 560 mg (4 capsules of 140 mg each) by mouth once daily for 12 cycles (each 28 days). If a subject demonstrates benefit from ibrutinib, therapy may be extended beyond 12 cycles at the previously established safe dose (i.e., typically the dose that the subject is on at the end of Cycle 12) until disease progression, discontinuation at the discretion of the investigators (for reasons specified in Section 5.4) or subject, or the drug is no longer available for investigational purposes, or a maximum duration of treatment of 2 years.

### 3.1.1. Study Schema






### 3.2. Study Design Rationale

As this is a phase 2 study with the goal of assessing efficacy, all enrolled subjects who meet inclusion criteria will be given the study medication. The high risk SMM group is incorporated since this is the subgroup most likely to progress to MM, often in the form of bone disease, and thus the group in which an intervention is most needed and most likely to be effective

The primary endpoint – the proportion of patients who remain in SMM and do not progress to symptomatic MM will be measured using objective criteria as per the most recent IMWG definitions of MM, with the exception of the serum free light chain criteria.[7] Given that the median time to progression in the high risk SMM patient population is about 2 years, our follow-up period should provide an indication of treatment effect.

In an ongoing study of ibrutinib as single agent or in combination with dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma, clinical benefit was seen with doses of 560 mg and 840 mg daily, and both dosages were well-tolerated overall whether in isolation or with dexamethasone.[33]

Correlative studies will aim to identify factors that predict for increased response to ibrutinib, and characterize changes that occur not only in myeloma cells, but also in the bone marrow microenvironment in response to ibrutinib therapy. Gene expression profiling of $CD138^+$ cells has shown prognostic value not only for patients with MM, but also in those with SMM, and this value is independent of variables such as M-protein and BM PC percentage.[39] We hypothesize that ibrutinib may alter the gene expression profile of SMM patients by virtue of the mechanisms described in Section 1.2. GEP assays will be performed on myeloma cells ($CD138^+$) and cells in the bone marrow microenvironment ($CD138^-$) to look for alterations. Additionally, ibrutinib has been found to inhibit interleukin-2-inducible kinase (ITK), an essential enzyme in Th2 T cells. This action alters the balance between Th1 and Th2 cells and can potentially enhance antitumor immune responses.[40,41] Immunologic assays to examine Th1/Th2 balance will examine this potential alternative mechanism of action.



# 4. SUBJECT SELECTION

## 4.1. Inclusion Criteria

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

*Disease Related*

1. High risk SMM, defined as bone marrow plasma cells between 10% and 60%, plus one of the following:
    a. High paraprotein burden: Serum M-protein ≥ 3 g/dL [except IgA ≥ 2 g/dL] or urine M-protein > 500 mg per 24 hours
    b. Moderate paraprotein burden: [(serum m protein < 3 g/dl but > 1 g/dl) or (urine m-protein > 200 mg/24h)] AND serum free light chain ratio < 0.126 or > 8
    c. involved to uninvolved free light chain ratio of > 100
    d. abnormal plasma cell phenotype ≥ 95% and immunoparesis (defined by a reduction below the lower limit of normal in 1 or 2 of the uninvolved immunoglobulins)
    e. evolving type of smoldering MM defined as
        i. :⩾10% Increase in serum M-protein and/or involved immunoglobulin level within the first 6 months of diagnosis (only if baseline M-protein was ⩾3 g/dl)

        *and/or*

        ii. ⩾25% increase in serum M-protein and/or involved immunoglobulin level within the first 12 months of diagnosis (for any level of M-protein) *plus minimum increase of* 0.5 g/dl in M-protein or 500 mg/dl in immunoglobulin or both
    f. presence of translocation (4;14) or deletion 17 p

2. Measurable disease, defined as: M-protein ≥ 1 g/dL OR Bence-Jones protein (BJP) > 200 mg/24 hr OR involved free light chain > 100 mg/dL
3. Diagnosed with SMM within the last 4 years

*Laboratory*

1. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening, with the exception of pegylated G-CSF (pegfilgrastim) and darbopoeitin which require at least 14 days prior to screening defined as:
    - Absolute neutrophil count > 750 cells/$mm^3$ (1.0 x $10^9$/L).
    - Platelet count > 75,000 cells/$mm^3$ (75 x $10^9$/L).
2. Adequate hepatic and renal function defined as:
    - Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN).
    - Estimated creatinine clearance ≥ 30 ml/min (Cockcroft-Gault)
    - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, in which case the total bilirubin should be < 3 x ULN)
3. PT/INR < 1.5 x ULN and PTT (aPTT) < 1.5 x ULN

*Demographic*

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

*Ethical/Other*

6. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥ 1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.
7. Male and female subjects must agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the period of therapy and for 30 days after the last dose of study drug.

### 4.2. Exclusion Criteria

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

*Disease-Related*

1. No end organ damage attributable to a plasma cell disorder, defined as having ANY of the following:
    a. Hypercalcemia: Serum calcium > 1 mg/dL above the upper limit of normal or > 11 mg/dL

   b. Renal insufficiency: Serum creatinine > 2 mg/dL or creatinine clearance < 30 mL per min
   c. Anemia: Hemoglobin value > 2 g/dL below the upper limit of normal or a hemoglobin value < 10 g/dL
   d. Bone lesions: One or more lytic lesions on skeletal radiography, CT, MRI, PET-CT, or PET-MRI
2. Bone marrow plasma cells < 10% or > 60%
3. Has received prior anti-myeloma therapy of any type
4. Has received prior bisphosphonate therapy
5. Osteoporosis, defined as T-score less than -2.5
6. On warfarin therapy or other vitamin K antagonists within 7 days of treatment initiation
7. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitors or inducer (see Appendix 3)
8. Has received an investigational drug, investigational vaccine, or has used an investigational medical device within 4 weeks or 4 half-lives, whichever is longer, before Cycle 1, Day 1 of study therapy

*Concurrent Conditions*

1. History of other malignancies, except:
   - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease
2. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc). Any use of corticosteroids EITHER for > 14 days OR at dosages > 20 mg/day of prednisone or equivalent is prohibited.
3. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug
4. Recent infection requiring systemic treatment that was completed ≤ 14 days before the first dose of study drug
5. Known bleeding disorders (eg, von Willebrand's disease) or hemophilia
6. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
7. Known HIV, HCV or HBV infection. 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.
8. Any uncontrolled active systemic infection

9. Major surgery within 4 weeks of first dose of study drug
10. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigators' opinion, could compromise the subject's safety or put the study outcomes at undue risk
11. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to start of first study treatment
12. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification [Appendix 6]
13. Unable to swallow capsules, malabsorption syndrome, prior resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, partial or complete bowel obstruction, or any other disease significantly affecting gastrointestinal function
14. Lactating or pregnant
15. Unwilling or unable to participate in all required study evaluations and procedures
16. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations)

# 5. TREATMENT OF SUBJECTS

## 5.1. Treatment allocation

This is an open-label study. Subjects will not be blinded to the study drug. All enrolled subjects will receive open-label ibrutinib capsules.

## 5.2. Study treatment

### 5.2.1. Route and schedule

Ibrutinib 560 mg once daily by mouth, given in capsules of 140 mg each.

## 5.3. Study Medications

### 5.3.1. Ibrutinib

#### 5.3.1.1. Formulation/Packaging/Storage

Ibrutinib will be provided by Pharmacyclics for this study. It is provided as hard gelatin capsules, each containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

Ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing information meeting applicable regulatory requirements. All study drug will be dispensed in child-resistant packaging. Ibrutinib will be dispensed in 30-day supplies during the first 4 cycles of the study. Thereafter, ibrutinib will be dispensed in 90-day supplies, since subject follow-up from that point onward is conducted in approximately 90-day intervals.

Refer to the site pharmacy manual and Investigator's Brochure for additional guidance on study drug storage, preparation and handling.

#### 5.3.1.2. Dose and Administration

Ibrutinib is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix 2).

To be eligible for treatment with ibrutinib whether at study initiation or at subsequent cycles, subjects must meet all laboratory criteria as listed in Section 4.1 and not meet any of the criteria for ibrutinib dose hold or modification per Section 5.3.1.4.

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

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned capsules must not be re-dispensed to anyone. Subjects will be required to maintain a dose diary, which will be provided (Appendix 4).

Duration of treatment is 12 cycles, each 28 days long. If a subject demonstrates benefit from ibrutinib, therapy may be extended beyond this duration at the established safe dose (i.e., typically the dose that the subject is on at the end of Cycle 12) until disease progression,

discontinuation by the investigators (for reasons listed in Section 5.4) or subject, or the drug is no longer available for investigational purposes, or a maximum during of 2 years from the beginning of therapy.

#### 5.3.1.3. 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 11 for further information regarding AE reporting.

#### 5.3.1.4. Dose Modification of Ibrutinib for Adverse Reactions

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

- Grade 4 ANC (< 500/µL) for more than 7 days. Neutrophil growth factors are permitted.
- Grade 3 thrombocytopenia (< 50,000/µL) in the presence of clinically significant bleeding events
- Grade 4 thrombocytopenia (< 25,000/µL)
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy
- Grade 3 or greater renal impairment OR creatinine clearance <30 mL/min
- Grade 2 or greater AST, ALT or total bilirubin level elevation in patients who had normal values at the time of study entry
- For subjects who develop mild hepatic impairment (Child-Pugh class A) or worse, follow the dosing guidance in Section 5.3.1.5
- Any other Grade 4 or unmanageable Grade 3 toxicity

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. Anticoagulants (excluding warfarin) or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (refer to Section 6.2.4).

**Table 1. Ibrutinib Dose Modifications**

| Occurrence | Action to be Taken |
|---|---|
| First | Withhold study drug until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower (ie, decrease dose by 140 mg/day) |
| Second | Withhold study drug until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower from dose at first occurrence (ie, decrease dose by another 140 mg/day) |
| Third | Discontinue study drug |

If complete resolution or improvement of the toxicity to Grade 1 or to baseline values is achieved within 28 days, the investigators may elect to have the subject restart treatment with study drug. If the toxicity takes more than 28 days to resolve, permanently discontinue study drug. Upon restarting treatment with study drug, follow the dose modifications for study drug according to Table 1.

#### 5.3.1.5. 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 above as needed.

### 5.4. Criteria for Permanent Discontinuation of Study Drug

The investigators will attempt to keep a subject who is experiencing clinical benefit (refer to Section 7) in the study unless significant toxicity puts the subject at risk, or routine noncompliance puts the study outcomes at risk. If the subject meets any of the following criteria, then withdrawal from the study treatment is mandatory:

- Subject has confirmed progression to MM defined as having any of the following:
  - Hypercalcemia: Serum calcium > 1 mg/dL above the upper limit of normal or > 11 mg/dL
  - Renal insufficiency: Serum creatinine > 2 mg/dL or creatinine clearance < 30 mL per min

- Anemia: Hemoglobin value > 2 g/dL below the upper limit of normal or a hemoglobin value < 10 g/dL
- Bone lesions: One or more lytic lesions on skeletal radiography, CT, MRI, PET-CT, or PET-MRI
- ≥ 60% bone marrow plasma cells
- Note that an increase in the involved: uninvolved FLCR to ≥ 100 will not be considered disease progression, in the absence of the above findings

- Subject has an intercurrent illness or AE that prevents further ibrutinib capsule administration
- Subject decides to withdraw from study
- Subject becomes pregnant
- Subject is noncompliant with study procedures and/or scheduled evaluations
- Subject requires a prohibited concomitant medication or bone marrow transplant
- Investigator considers withdrawal to be in the best interest of the subject
- Pharmacyclics requires that the subject withdraw
- Regulatory authorities terminate the study
- Subject completes the study (although as per Section 5.3.1.2 subjects who benefit from study treatment may receive additional supply until disease progression or a maximum of 2 years of treatment)

Subjects who withdraw for any reason after receiving the first dose of ibrutinib will not be replaced. Subjects who withdraw prior to the first dose of ibrutinib may be replaced.



# 6. CONCOMITANT MEDICATIONS/PROCEDURES

## 6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Transfusions may be given in accordance with institutional policy.

Short courses (≤ 14 days) of steroid treatment for non-cancer related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and medication reactions) at doses that do not exceed 20 mg per day of prednisone or equivalent are permitted.

## 6.2. Medications to be Used with Caution

### 6.2.1. CYP3A- Inhibitors/Inducers

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

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

- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg (for 840 mg/day dose, reduce to 280 mg) for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).

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

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

A list of common CYP3A inhibitors and inducers is provided in Appendix 3. A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

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

### 6.2.2. QT Prolonging Agents

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

### 6.2.3. Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries, see Section 6.4.

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

### 6.3. Prohibited Concomitant Medications

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

Corticosteroids for > 14 days or at doses > 20 mg/day of prednisone or equivalent are prohibited.

### 6.4. Guidelines for Ibrutinib Management with Surgeries or Procedures

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

#### 6.4.1. Minor Surgical Procedures

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

#### 6.4.2. Major Surgical Procedures

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

#### 6.4.3. Emergency Procedures

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



## 7. STUDY EVALUATIONS

### 7.1. Description of Procedures

The Schedule of Assessments is provided in Appendix 1. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 5. Before study entry, throughout the study, and at the follow-up evaluations, various clinical and diagnostic evaluations will be performed. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability, and to assess treatment response.

Any of the clinical evaluations and laboratory studies below may be repeated more frequently if clinically indicated.

### 7.1.1. Physical Examination, Height and Weight

All physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

### 7.1.2. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

### 7.1.3. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG Performance Status is provided in Appendix 6.

### 7.1.4. Laboratories

All studies are to be performed at the local laboratory (Mount Sinai) unless otherwise indicated.

#### 7.1.4.1. CBC with differential

Parameters will include white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands (if reported). These parameters will be checked as outlined in the Schedule of Assessments and as clinically indicated.

#### 7.1.4.2. Serum chemistries

These will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, total protein, AST, ALT, alkaline phosphatase, total bilirubin. These studies will be checked as outlined in the Schedule of Assessments and as clinically indicated. Additionally, lactate dehydrogenase (LDH), phosphorous, magnesium, and uric acid will be checked at Screening, and will not be repeated unless abnormal.

#### 7.1.4.3. Coagulation studies

Measurement of prothrombin time, international normalized ratio, and activated partial thromboplastin time will be performed at Screening. They will be repeated at Cycle 2 to ensure stability.

#### 7.1.4.4. Urinalysis

This is to be checked at Screening and includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

#### 7.1.4.5. Pregnancy Test

Pregnancy testing (urine or serum) is required at Screening for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible. This test is to be repeated as per the Schedule of Assessments and as clinically indicated for women of childbearing potential.

#### 7.1.4.6. Serum and Urine Protein Electrophoresis

Samples will be collected at Screening, and prior to study treatment administration on Day 1 of Cycle 1. Additional sample collection per Section 8.2.

#### 7.1.4.7. Serum Free Light Chain Assay

Samples will be collected at Screening, and prior to study treatment administration on Day 1 of Cycle 1. Additional sample collection per Section 8.2.

#### 7.1.4.8. Serum and Urine Immunofixation

Samples will be collected at Screening, and prior to study treatment administration on Day 1 of Cycle 1. Additional sample collection per Section 8.2.

#### 7.1.4.9. Quantitative Serum Immunoglobulins (IgA, IgG, IgM)

Samples will be collected on Screening, and prior to study treatment administration on Day 1 of Cycle 1. Additional sample collection per Section 8.2.

#### 7.1.4.10. Serum β2-microglobulin

Samples will be collected at Screening and at End of Treatment.

#### 7.1.4.11. 25-hydroxy vitamin D

Samples will be collected at Screening and at End of Treatment.

#### 7.1.4.12. Biomarkers

Biomarkers (serum CTX, urinary NTx, serum DKK-1, serum RANKL, serum MIP-1α, serum SDF-1) of bone metabolism and myeloma disease activity (IL-6) will be tested. Blood and urine samples will be collected on Cycle 1 Day 1, Cycle 7 Day 1, at every subsequent 24 weeks for subjects who continue on study, and at End of Treatment. Serum CTX and urinary NTx will be sent to Quest Diagnostics for analysis. The remaining specimens will be sent to Pharmacyclics.

#### 7.1.4.13. Genomic and immunologic correlatives

Serum and bone marrow (6 mL each) will be collected and stored for genomic and immunologic correlative studies. Specimen collection will be performed on Screening, Day 1 of Cycle 7, and at End of Treatment. These samples may be characterized by technologies such

as gene expression profiling, targeted sequencing for genomic alterations, and intracellular signaling pathway analysis. Inhibition of BTK and other related kinases may also be explored. These efforts may identify genes and pathways associated with primary or later development of resistance to ibrutinib and potentially identify biomarkers that could assist with future development of this compound. Pharmacodynamic assays, ie, BTK occupancy, may be performed to correlate results of biomarker assessments to the physiological effects of ibrutinib.

### 7.1.5. Diagnostics/Procedures

#### 7.1.5.1. Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be performed at Screening. It may be repeated at any subsequent time during the study, as determined necessary by the investigators. Subjects should rest in a supine position before ECG collection and should refrain from talking or moving arms or legs.

#### 7.1.5.2. Bone marrow aspiration and biopsy

A unilateral bone marrow aspirate and biopsy will be obtained at Screening, at Cycle 13 Day 1, and at the End of Treatment. Specimens will be submitted to the Mount Sinai Department of Pathology laboratory to determine bone marrow involvement and evaluate morphology. Fluorescent in situ hybridization (FISH) will be performed to allow for identification of abnormalities such as t(4;14), t(11;14) and del 17p. An additional 6 mL of bone marrow aspirate will be collected for genomic and immunologic assessments (refer to Section 7.1.4.13).

#### 7.1.5.3. Bone radiological assessment

A radiologic skeletal survey, PET-MRI, DEXA scan, and qCT with FEA are required at Screening. PET-MRI, DEXA, and qCT are to be repeated at End of Treatment. A skeletal survey includes a lateral radiograph of the skull, antero-posterior and lateral views of the spine, and antero-posterior views of the pelvis, ribs, femora, and humeri. Bone radiological assessments are to be done within 42 days of Screening. Additional imaging can be performed as clinically indicated at any time during the study, as determined necessary by the investigators.

## 7.2. Efficacy Evaluations

Efficacy evaluations will be conducted at the beginning of Cycles 4, 7, 10, and every 3 months thereafter for subjects who do not progress to myeloma, and at End of Treatment. Response assessments will be made using IMWG response criteria (refer to Appendix 3).

All Screening, Cycle 1 Day 1 and End of Treatment assessments will include quantitative immunoglobulins, serum and urine electrophoresis, serum and urine immunofixation, and serum free light chain assay. Other assessments may entail more limited testing, in that only the parameters that are required for a particular response category will be assessed. If at any time CR is suspected, all assessments including serum, urine, radiographic imaging (if applicable) and bone marrow biopsy must be performed as per the IMWG response assessment guidelines.

1. If SPEP and UPEP both meet criteria, both will be performed at assessment.
2. If only SPEP meets criteria, then only SPEP will be required at each assessment.
3. If only UPEP meets criteria, then only UPEP will be required at each assessment.
4. If neither SPEP nor UPEP meet criteria, then only sFLC assay will be required at each assessment.

At the investigators' discretion, additional evaluations may be performed but they are not to be used for response assessment.

### 7.2.1. Survival and subsequent anticancer therapies

#### 7.2.1.1. Survival

After disease progression, subjects will be contacted to assess survival status every 12 weeks (± 14 days) from End of Treatment visit until death, subject withdrawal of full consent, subject loss to follow-up, study termination by investigator, or 3 years after the last subject is enrolled, whichever comes first. At the time of the analysis and at study closure, a survival sweep will be conducted. All subjects who are not known to have died or withdrawn consent prior to the survival sweep will be contacted at that time.

#### 7.2.1.2. Subsequent Anticancer Therapies

After study treatment is complete, the following information on subsequent anticancer therapies will be collected every 12 weeks (± 14 days) from End of Treatment Visit until death, subject withdrawal of full consent, subject loss to follow-up, study termination by investigator, or until 3 years after the last subject is enrolled, whichever comes first:

- Receipt of subsequent anticancer therapies
- Indication for initiation of subsequent anticancer therapy
- Response to subsequent anticancer therapies

## 7.3. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the CRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix 1) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the laboratory manual that will be provided for sample collection and handling.

# 8. STUDY PROCEDURES

All laboratory and radiographic testing is to be performed at Mount Sinai unless otherwise noted.

## 8.1. Screening Phase

All routine laboratory and clinical screening assessments must be performed within 28 days before the first administration of study drug. A longer window of 42 days is allowed for bone marrow and radiologic studies. All study-specific assessments that are not part of standard-of-care must be done after subjects sign the ICF. The following are required:

**Confirmation of Eligibility:** Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion (refer to Section 4). De-identified copies of measurable disease as documented by SPEP, serum FLC and UPEP is required prior to enrollment. SMM diagnosis will be confirmed and documented.[42]

**Medical History:** The subject's complete medical history will be collected and recorded through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities.

**Concomitant Medications and Therapy:** All concomitant medications and procedures will be collected and recorded prior to the start of study drug.

**Physical Examination, Vital Signs, Height, and Weight:** The screening physical examination (PE) will include, at a minimum, the general appearance of the subject, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed.

**ECOG Performance Status:** The ECOG index is provided in Appendix 6.

**Electrocardiogram:** Subjects should be in the supine position when this is performed.

**Bone Marrow Aspirate and Biopsy:** A unilateral bone marrow aspirate and biopsy documenting percent marrow involvement by plasma cells will be done at Screening. Part of the aspirate will be sent for flow cytometry, FISH, and cytogenetic studies. Flow cytometry should include immunophenotyping for SMM risk stratification. Specimens will be reviewed by a pathologist at Mount Sinai.

**Other Laboratory Tests:** Hematology and serum chemistry are part of the screening procedures to ensure eligibility. For a description of these tests, refer to Section 7.1.4.

**Urinalysis:** Includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

**Pregnancy Test:** Required only for women of childbearing potential. Can be performed using either serum or urine. If positive, pregnancy must be ruled out by ultrasound to be eligible for participation in the study.

**Coagulation Studies:** Measurement of PT, INR, and aPTT are part of the screening procedures.

**Bone Radiological Assessment:** A radiologic skeletal survey, PET-MRI, DEXA scan, and QCT with FEA are required. Bone radiological assessment includes a lateral radiograph of the skull, antero-posterior and lateral views of the spine, and antero-posterior views of the pelvis, ribs, femora, and humeri. QCT with FEA should cover the same body areas as well. Bone radiological assessments are to be done within 42 days of Screening.

**Myeloma Specific Tests:** Include serum and urine protein electrophoresis, quantitative immunoglobulins, serum free light chain assay, serum and urine immunofixation, and β2-microglobulin. For a description of these tests, refer to Section 7.1.

### 8.2. Treatment Phase

Each cycle is defined as 28 days of continuous therapy with ibrutinib. Study visits will occur on Cycle 1 Day 1 and thereafter on Day 1 (±3 days) of Cycles 2, 3, 4, 7, 10. For subjects who continue receiving ibrutinib beyond Cycle 12, study visits will continue to occur every 3 cycles (ie, Cycle 13, 16, 19, etc) until therapy is stopped, at which point the End of Treatment visit will occur. Refer to the Schedule of Assessments (Appendix 1) for a complete list of procedures performed at each of the scheduled study visits.

**Concomitant Medications and Therapy:** Concomitant medications and therapy will be recorded at each visit. Refer to Section 6 for a listing of permitted medications.

**Adverse Events:** The definition for an AE is provided in Section 11.1. All medical occurrences from the time of the first administration of study drug that meet this definition must be recorded. Important additional requirements for reporting SAEs are included in Section 11.3. AEs will be recorded at each visit, or as they occur during the treatment period.

**Physical Examination, Vital Signs, and Weight:** Symptom-directed physical exams will be performed during the treatment period. Vital signs and weight will be measured and recorded at each study visit.

**ECOG Performance Status:** The ECOG performance status will be measured and recorded at each study visit. The ECOG index is provided in Appendix 2.

**Bone Marrow Aspirate and Biopsy:** A unilateral bone marrow aspirate and biopsy documenting percent marrow involvement will be repeated on Cycle 7 Day 1, at End of Treatment, and additionally at the discretion of the investigator. There is a window of ± 14 days at each of these time points for performing the procedure. Part of the aspirate will be sent for

flow cytometry, FISH, and cytogenetic studies. Flow cytometry should include immunophenotyping for SMM risk stratification.

**Hematology:** Hematology parameters will be measured on Day 1 of Cycles 1, 2, 3, 4, 7, and 10. For subjects who continue receiving ibrutinib beyond Cycle 12, labs will continue to occur every 3 cycles (ie, Cycle 13, 16, 19, etc.) until therapy is stopped, at which point an End of Treatment collection will occur. Specimens can be collected additionally as felt clinically indicated by the investigators. Hematology parameters must include complete blood count (CBC) with differential and platelet counts.

**Serum Chemistries:** Chemistry parameters include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, and total protein. Serum chemistry parameters will be measured on Day 1 of Cycles 1, 2, 3, 4, 7, and 10. For subjects who continue receiving ibrutinib beyond Cycle 12, labs will continue to occur every 3 cycles (ie, Cycle 13, 16, 19, etc.) until therapy is stopped, at which point an End of Treatment collection will occur. Specimens can be collected additionally as felt clinically indicated by the investigators.

**Coagulation Studies:** The PT, INR, and aPTT will be checked on Cycle 2 to ensure values remain stable compared to screening values. Specimens can be collected additionally as felt clinically indicated by the investigators.

**Myeloma-specific Tests:** Myeloma-specific tests include M-protein quantification by SPEP and UPEP, serum and urine immunofixation, serum free light chain, quantitative immunoglobulins, and β2-microglobulin. UPEP is performed on a timed urine collection and should be recorded as normalized to 24 hours. Urine creatinine determinations should be performed as well as UPEP on all urines collected for M-protein quantification.

**Biomarkers:** Biomarkers of bone turnover (serum CTX, urine NTx, urine NDKK-1, RANKL, SDF-1, MIP-1α) and myeloma disease activity (IL-6) will be assayed on Cycle 7 Day 1. If a subject continues on treatment beyond 12 cycles or continues on follow-up without treatment, these tests will continue to be checked at every 24 week intervals (eg, Cycle 13, 19, etc). These labs will also be assessed at End of Treatment. Serum CTX and urinary NTx will be sent to Quest Diagnostics for analysis. The remaining specimens will be sent to Pharmacyclics for testing. Refer to the laboratory manual for instructions on collecting and processing these samples.

**Bone Radiological Assessment:** A repeat DEXA, PET-MRI and QCT with FEA are to be performed at End of Treatment. Other bone radiological assessments are not mandated by the protocol, but should follow institutional guidelines and clinical discretion. These other assessments can entail radiography, MRI, or PET/CT of any or all axial and appendicular skeleton.

**Missed Evaluations:** Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigators' opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

**End of Treatment:** The End of Treatment is defined as end of ibrutinib therapy. The End of Treatment visit should occur 30 days (±10 days) after the last administration of ibrutinib.

### 8.3. Follow-up Phase

The Follow-up Phase will begin once subjects discontinue treatment for reasons other than disease progression. For example, subjects could have completed the planned number of cycles, or have been prematurely discontinued from study treatment. Reasons for premature discontinuation of study treatment are listed in Section 5.4. Subjects will continue in Follow-Up Phase until they require therapy for symptomatic MM, study closure, loss to follow-up, or withdrawal of consent, whichever occurs sooner. They will continue to have disease evaluations as indicated by the Schedule of Assessments, with a +/- 1 month window on evaluations permitted for flexibility. If subjects have not progressed to symptomatic MM, no other anti-myeloma therapies are allowed during the study.

Any follow-up information that is obtained via telephone contact must be documented in writing.

## 9. SUBJECT COMPLETION AND WITHDRAWAL

### 9.1. Completion

The expected duration of this study is approximately 3 years. The study is considered completed when the last assessment for the last subject participating in the study is performed, the Principal Investigator decides to terminate the study, or all subjects are rolled over to a long-term safety study.

### 9.2. Withdrawal from Study

Subjects may be withdrawn from the study at any time at the investigators' discretion. The reason for withdrawal will be clearly documented and recorded on the case report form. Common reasons for withdrawal include:

- Patient withdrawal of consent or refusal to take study medication
- Patient noncompliance: any significant non-medical deviation from the study protocol without prior agreement of the investigators

- Disease progression: see Section 5.4
- Toxicity: following a severe or life-threatening adverse reaction at the discretion of the treating physician
- Prohibited medication: treatment with other chemotherapy or investigational agents is not allowed and will result in the patient's removal from the study
- Investigators' discretion: patients may be discontinued from the study at any time at the investigators' discretion

# 10. STATISTICAL METHODS AND ANALYSIS

## 10.1. Subject Information

All enrolled subjects who received at least one cycle of study treatment will be used for statistical analysis.

## 10.2. Endpoints

### 10.2.1. Primary Endpoints

The primary endpoint in this study is the proportion of patients with high risk smoldering multiple myeloma who do not progress to symptomatic myeloma by IMWG criteria after 12 cycles (each 28 days) of ibrutinib therapy.

### 10.2.2. Secondary Endpoints

#### 10.2.2.1. Overall response rate

The proportion of patients who achieve a partial response or better (as defined by IMWG criteria) will be reported.

#### 10.2.2.2. Bone Density

Changes in bone density and qCT after 12 cycles of ibrutinib therapy will be measured.

#### 10.2.2.3. PET-MRI

Changes in PET-MRI findings after 12 cycles of ibrutinib therapy will be measured.

#### 10.2.2.4. Bone-related Biomarkers

Changes in bone related biomarkers in urine and serum after 12 cycles of ibrutinib therapy will be measured and reported.

#### 10.2.2.5. Genomic and Immunologic Correlatives

A separate but companion correlative study will examine possible baseline predictors of response as well as alterations associated with ibrutinib therapy at the genomic and immunologic levels.

### 10.3. Sample Size Determination

**Null hypothesis:** Approximately 25% of high risk SMM are expected to progress at 1 year.

**Alternative hypothesis:** Given that the disease stabilization rate on ibrutinib monotherapy was 30% in relapsed or relapsed/refractory MM patients with a median of 4 prior therapies (range 2-14), we hypothesize that for a treatment naïve high risk SMM population, ibrutinib monotherapy will stabilize disease progression in most patients and only 10% of patients will progress at 1 year.

Utilizing a Simon's two-stage design, we will test the null hypothesis that the true response rate is 75% against a one-sided alternative that the response rate is 90%[43]. Using a Simon's two-stage design, we plan to enroll 15 patients in the first stage. If 4 or more patients progress to symptomatic MM, enrollment to this cohort will be stopped for futility. Otherwise, an additional 21 patients will be accrued, for a total sample size of 36. The null hypothesis will be rejected if 30 or more responses are observed in 36 patients. This design yields a type I error rate of 15% and power of 90% when the true response rate is 90%.

### 10.4. Efficacy Analysis

The rate of stable disease or better (PR, VGPR, CR, sCR; refer to Appendix 4) as per IMWG definitions after 12 cycles of ibrutinib therapy will be reported as a percentage of the total number of subjects that are analyzable. A 90% exact confidence interval for the rate will be computed using the Clopper and Pearson method. A 2-year PFS rate will be estimated using the Kaplan-Meier method and a 2-sided, 90% asymptotic confidence interval for the rate will be computed using Greenwood's formula for the variance of a time-to-event rate.

The final analyses of all endpoints, except those involving progression, will be conducted 6 months after the last subject is enrolled. The final analyses of progression-based endpoints, such as estimating the 2-year PFS rate and estimating the PFS distribution, will be conducted at the end of the study, which will occur after either all subjects have progressed or died or 3-years after the initiation of therapy of the last subject enrolled, whichever occurs first.

### 10.5. Safety Analysis

Sequential boundaries will be used to monitor the toxicity rate (all event terms of Grade 3 or greater). The accrual will be halted if excessive numbers of toxicities are seen, that is, if the

number of toxicities is equal to or exceeds $b_n$ out of $n$ patients with full follow-up (see table). Consideration will be given to restarting treatment at a decreased dose level based upon a risk to benefit analysis for all enrolled subjects to date. If such a change is to be considered, then a protocol amendment will be submitted accordingly. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 5% when the rate of dose-limiting toxicity is equal to the acceptable rate of 30%.

| **Number of Patients, *n*** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Boundary, $b_n$ | - | - | - | 4 | 5 | 5 | 6 | 6 | 7 | 7 | 8 | 8 | 9 | 9 | 10 | 10 | 11 | 11 | 11 | 12 |
| **Number of Patients, *n*** | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |
| Boundary, $b_n$ | 12 | 13 | 13 | 13 | 14 | 14 | 15 | 15 | 15 | 16 | 16 | 17 | 17 | 17 | 18 | 18 | 19 | 19 | 19 | 20 |
| **Number of Patients, *n*** | 41 | 42 | 43 | 44 | 45 | 46 | | | | | | | | | | | | | | |
| Boundary, $b_n$ | 20 | 21 | 21 | 21 | 22 | 22 | | | | | | | | | | | | | | |

Adverse events will be categorized using the latest version of MedDRA and will be graded using CTCAE v4.0. Laboratory values will also be graded using CTCAE v4.0. Worst grade of adverse events will be tabulated by System Organ Class and Preferred Term. Shift from baseline to worst on-study value will be tabulated for hematologic and serum chemistry laboratory examinations. These analyses will be done on the population of treated subjects, and presented separately by cohort.

### 10.6. Biomarker Analyses

Levels of the biomarkers IL-6, SDF-1, RANKL, MIP-1α, CTX, NTx will be collected and reported by their means with standard deviations before and after ibrutinib therapy.

## 11. ADVERSE EVENT REPORTING

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

### 11.1. Definitions

#### 11.1.1. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal

laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

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

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

Adverse events may include, but are not limited to:

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

The following are NOT considered AEs:

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

### 11.1.2. Serious Adverse Events

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

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

### 11.1.3. Severity Criteria (Grade 1-5)

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

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment

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

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

### 11.1.4. Causality (Attribution)

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

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

## 11.2. Unexpected Adverse Events

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

## 11.3. Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

### 11.3.1. Assessment of Adverse Events

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

### 11.3.2. Adverse Event Reporting Period

All serious AEs will be captured from the time the ICF is signed and dated to the first dose of the study drug. Subsequently, all AEs whether serious or non-serious will be captured until 30 days following the last dose of study drug.

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

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported (See Section 11.1.1).

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, the investigators' evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

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

### 11.3.3. Pregnancy

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

A female subject must immediately inform the investigators if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the investigator if his partner becomes pregnant from the time of consent to 3 months

after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The investigators 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 the Tisch Cancer Institute Data and Safety Monitoring Committee, the IRB, and Pharmacyclics, 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. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old and this must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

### 11.3.4. Other Malignancies

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

### 11.3.5. Eye-Related Adverse Events

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

### 11.3.6. Adverse Events of Special Interest (AESI)

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

#### 11.3.6.1. Major Hemorrhage

**Major hemorrhage is defined as any of the following:**

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

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE. '*Events meeting the definition of major hemorrhage will be captured as an event of special interesting according to Section 11.3.6 above.*'

### 11.3.7. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) 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 15 days of the event. Pharmacyclics may request follow-up and other additional information from the investigator.

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

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

**Reporting to Regulatory Agencies:**

Serious adverse events will be reported to the FDA by the IND Sponsor (Mount Sinai) according to 21 CFR 312.32. In the event of any such events, the study will be stopped until the event is thoroughly investigated and reviewed with the FDA.

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



## 12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

### 12.1. Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the International Conference on Harmonization Harmonized Tripartite Guidelines for Good Clinical

Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

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

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

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

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

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

### 12.3. Informed Consent

The ICF and process must comply with the United States regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the investigator or his/her designee provides to the subject and the subject's agreement to participate. The investigator, or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the study, the study procedures, anticipated benefits, potential risks, the possible adverse effects, and any discomfort participation in the study may entail. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed (such as screening). The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by the study investigators at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

### 12.4. Quality Control and Quality Assurance

The investigators shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (§21 CFR Parts 11, 50, 54, 56, and

312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

### 12.5. Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 12.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific Health Insurance Portability and Accountability Act consent may be used). The investigators or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/IECs. As the study sponsor, the investigators will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigators' or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigators' responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

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

### 12.6. Study Files and Record Retention

The investigators and other appropriate study staff are responsible for maintaining all essential documentation relevant to the study. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosure, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections; SAE forms transmitted to Pharmacyclics and notification of SAEs and related reports, source documentation, normal laboratory values; decoding procedures for blinded studies; curricula vitae for study staff, all relevant correspondence, and other documents pertaining to the conduct of the study.

Subject identity information will be maintained for 15 years. All other essential documentation will be retained by the investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

Pharmacyclics must be notified in advance of any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party.

## 12.7. Case Report Forms and Record Maintenance

Electronic case report forms (eCRFs) will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority form) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigators will ensure that the eCRFs are accurate, complete, legible, and completed as soon as reasonably possible. At all times, the investigators have final responsibility for the accuracy and authenticity of all clinical data. Study staff will be appropriately trained in the use of eCRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRFs is true by providing electronic signature within the EDC system.

## 12.8. Investigational Study Drug Accountability

### 12.8.1. Receipt of Study Drug

The Principal Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Pharmacyclics or its representative.

### 12.8.2. Storage

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

### 12.8.3. Unused Study Drug Supplies

Pharmacyclics will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Pharmacyclics. Patients will be instructed to return empty bottles or unused capsules.

## 12.9. Study Monitoring/Audit Requirements

The investigator will monitor this study until completion. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to endure the quality and integrity of the data. This study is also subject to reviews or audits.

During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included on the ICF and permission from authorizing the use of protected health information.

## 12.10. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Data Safety Monitoring Board

Data and safety will be monitored by an internal Data and Safety Monitoring Board (DSMB) chaired by the PI. Other members of the committee will include co-investigators, the myeloma research program manager, and clinical research coordinators. All of these individuals have experience in clinical care as well as clinical research and monitoring of subjects with multiple myeloma. A statistician will also serve as a member of the committee.

Expected events in a population of patients with smoldering multiple myeloma include progression to multiple myeloma (as evidenced by hypercalcemia, renal insufficiency, anemia, lytic bone lesions, and ≥ 60% bone marrow plasma cells), infections, and venous thromboembolism. These events will be monitored for frequency and severity. If the investigators become aware that an otherwise expected adverse event has increased in severity or frequency, these will be promptly reported to the Tisch Cancer Institute (TCI) Data and Safety Monitoring Committee (DSMC), the IRB, and Pharmacyclics as an unexpected event. All deaths and any unanticipated serious adverse events will be reported to these three groups as well as to the FDA. The study will be stopped until the event has been fully evaluated and discussed with the FDA.

The myeloma research program manager will log and track all adverse events (graded by NCI

CTC criteria), subject enrollment, and protocol compliance. These findings will be systematically reviewed by the DSMB after the first three patients have completed 3 months of study treatment and thereafter every four months. A written report of the DSMB's findings will be generated. This report will be sent to the TCI DSMC. If the DSMB determines that due to safety or concern about lack of efficacy the study must be halted or the protocol modified, the TCI DSMC, IRB, and Pharmacyclics will be promptly notified and provided a copy of the written report.

### 12.11. Protocol Amendments

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

### 12.12. Publication of Study Results

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

### 12.13. Study Discontinuation

Per the IST Contract, the Principal Investigator reserves the right to terminate the study at any time. Should this be necessary, the Principal Investigator will arrange discontinuation procedures in partnership with Pharmacyclics. In terminating the study, the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests. Pharmacyclics may terminate the study for reasons including, but not limited to: evidence that the PI or an involved investigator is unqualified to conduct research or fulfill sponsor responsibilities (e.g., is listed on a debarment or ineligible investigator list); failure to meet timelines or achieve agreed upon milestones; a known or perceived risk to patient well-being is identified; or breach of contract. Additional grounds for termination are outlined in the IST Agreement.

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# 14. APPENDICES

## 14.1. Appendix 1. Schedule of Assessments

| Study procedure | | Treatment period[1] | | | | | | End of Treatment (EOT)[2] | Follow-up visits[3] |
|---|---|---|---|---|---|---|---|---|---|
| Cycle (= 28 days) | Screening | 1 | 2 | 3 | 4 | 7 | 10 and beyond[4] | | |
| Day | | 1[5] | 1 | 1 | 1 | 1 | 1 | | |
| Window | ≤ 28 days before start[6] | ± 3 days | | | | | | ± 10 days | |
| **PROCEDURES** | | | | | | | | | |
| Informed consent | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | |
| Height | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| ECOG performance status | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X |
| Adverse events assessment | X | X | X | X | X | X | X | X | X |
| Vital signs, including weight | X | X | X | X | X | X | X | X | X |
| Physical exam | X | X | X | X | X | X | X | X | X |
| Bone marrow aspirate, biopsy, flow cytometry, cytogenetics/FISH, and banking for correlatives[7] | X | | | | | xError! Bookmark not defined. | | X | |
| ECG[8] | X | | | | | | | | |
| **LABORATORY STUDIES** | | | | | | | | | |
| CBC, with differential | X | X | X | X | X | X | X | X | X |
| Chemistries[9] | X | X | X | X | X | X | X | X | X |
| Magnesium, phosphorus, LDH, uric acid | X | | | | | | | | |
| Lipid panel | X | | | | | | | | |
| PT, PTT, INR | X | | X | | | | | | |
| Urinalysis | X | | | | | | | | |
| B-2 microglobulin | X | | | | | | | X | |
| 25-hydroxy vitamin D[10] | X | | | | | | | X | |
| Pregnancy test (blood or urine)[11] | X | X | X | X | X | X | X | X | |
| Serum M-protein (SPEP) | X | X | | | X | X | X | X | X |
| Serum quantitative immunoglobulins | X | X | | | X | X | X | X | X |
| Serum free light chain assay | X | X | | | X | X | X | X | X |
| Serum immunofixation[12] | X | X | | | | | | X | X |
| Urine immunofixation[12] | X | X | | | | | | X | X |
| 24-hr urine protein electrophoresis (UPEP)[12,13] | X | X | | | X | X | X | X | X |
| Biomarkers: DKK-1, IL-6, SDF-1, RANKL, MIP-1α, CTX, urinary NTx, and banking for correlatives[14] | | X | | | | X | | X | X[15] |
| **IMAGING STUDIES** | | | | | | | | | |
| PET-MRI | X | | | | | | | X[16] | |
| Skeletal survey | X | | | | | | | | |
| DEXA scan[17] | X | | | | | | | X[18] | |

[1] No study assessments are planned for the following cycles: 5, 6, 8, 9, 11, 12. If treatment is continued beyond 12 cycles, then study visits will occur once every 3 cycles (eg, 13, 16, 19, etc).
[2] Occurs 30 days (±10 days) after the last administration of study treatment.
[3] For subjects who discontinue treatment for reasons other than disease progression. Continues until subject requires therapy for symptomatic MM or study closure, whichever occurs sooner. These assessments will be performed every 12 weeks apart. A +/- 1 month window for these visits is permitted for flexibility
[4] Patients who benefit from therapy will continue on ibrutinib beyond 12 cycles until evidence of disease progression up to a maximum of 24 cycles. They will be assessed every 3 cycles – ie, C13D1, C16D1, C19D1, C22D1, etc.
[5] Labs required for this cycle (Cycle 1) do not need to be repeated if done within 7 days prior to C1D1.
[6] Any bone marrow aspirate and biopsy, and imaging studies that were performed within 42 days of screening will be acceptable for screening purposes and will not need to be repeated.
[7] If the patient has had a bone marrow biopsy and aspirate done within 42 days of the Screening Visit, then this test does not need to be repeated. Flow cytometry should include immunophenotyping for SMM risk stratification. Cytogenetics and FISH studies should be repeated only if clinically indicated for the C7D1 and EOT time points. Each time that bone marrow is harvested, an additional 6 mL of aspirate should be collected in a green-top tube (containing heparin) and sent to the lab of Dr. Samir Parekh for analysis of genomic and immunologic correlatives.
[8] Performed with patient lying in supine position.
[9] Chemistries include: sodium, potassium, chloride, bicarbonate, BUN, creatinine, albumin, total protein, total bilirubin, alkaline phosphatase, AST, ALT, calcium. Using the creatinine, the patient's creatinine clearance (CrCl) will be calculated using the Cockcroft-Gault formula.
[10] May be repeated at additional time intervals as felt clinically indicated.
[11] Pregnancy testing is required for women of childbearing potential. The Cycle 1 Day 1 testing may be omitted if the screening test was performed within 72 hours prior. A positive result will result in disqualification or discontinuation from the study.
[12] May not need to be performed at all indicated visits - more limited testing is possible for certain patients. Refer to Section 7.2 for more information.
[13] Required for patients who have disease detectable in urine to confirm IMWG responses of VGPR or better. .
[14] Biomarkers to be drawn prior to administration of ibrutinib. Serum CTX and urinary NTx will be sent to Quest Diagnostics. The other biomarker tests will be sent to PCYC. In addition, 6 mL of blood should be collected in a green-top tube and banked for analysis of genomic and immunologic correlatives.
[15] Note that these labs will be checked every 24 weeks, instead of every 12 weeks as specified for the other labs.
[16] Repeat PET-MRI is to be performed after 12 cycles of therapy.
[17] T-scores for the following areas will be recorded: lumbar spine, femoral neck (both sides), total hip, forearm/radius. The lowest (most negative) T-score amongst all recorded values will be used to determine 'osteopenia' and 'osteoporosis.' Osteopenia is defined as a T-score between -1.0 and -2.5. Osteoporosis is defined as a T-score lower than -2.5.
[18] To be performed only in patients who have received at least 6 cycles of treatment.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| QCT with FEA | X | | | | | | X[18] | |

## 14.2. Appendix 2. Inhibitors and Inducers of CYP3A

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

| Inhibitors of CYP3A | Inducers of CYP3A |
|---|---|
| **Strong inhibitors:** | **Strong inducers:** |
| Indinavir | Avasimibe |
| Nelfinavir | Carbamazepine |
| Ritonavir | Phenobarbital |
| Clarithromycin | Phenytoin |
| Itraconazole | Rifampin |
| Ketoconazole | Rifabutin |
| Nefezodone | St. John's Wort |
| Saquinavir | **Moderate inducers:** |
| Suboxone | Bosentan |
| Telithromycin | Efavirenz |
| Cobicistat | Etravirine |
| Boceprevir | Modafinil |
| Mibefradil | Nafcillin |
| Telaprevir | **Weak inducers:** |
| Troleandomycin | Amprenavir |
| Posaconazole | Aprepitant |
| **Moderate inhibitors:** | Armodafinil |
| Aprepitant | Clobazamechinacea |
| Amprenavir | Glucocorticoids |
| Amiodarone | Nevirapine |
| Atazanavir | Oxcarbarzepine |
| Ciprofloxacin | Pioglitazone |
| Crizotinib | Rufinamide |
| Darunavir/ritonavir | Troglitazone |
| Dronedarone | Vemurafenib |
| Erythromycin | |
| Diltiazem | |
| Fluconazole | |
| Fosamprenavir | |
| grapefruit juice | |
| Seville orange juice | |
| Verapamil | |
| Voriconazole | |
| Imatinib | |
| **Weak inhibitors:** | |
| Cimetidine | |
| Fluvoxamine | |
| **All other inhibitors:** | |
| Chloramphenicol | |
| Delaviridine | |
| diethyl-dithiocarbamate | |
| Gestodene | |
| Mifepristone | |
| Norfloxacin | |

| |
|---|
| Norfluoxetine<br>star fruit |

## 14.3. Appendix 3. IMWG Uniform Response Criteria[44]

| RELAPSE CRITERIA |
|---|
| **sCR (Stringent complete response)** |
| CR as defined below AND normal FLC ratio AND absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence |
| **CR (Complete response)** |
| No M-protein in serum and urine by immunofixation AND no current evidence of soft tissue plasmacytomas AND ≤ 5% plasma cells in the bone marrow<br><br>In patients who lack measurable M-proteins in the serum and urine being monitored using FLC levels, the definition of CR requires a normalization of the FLC ratio in addition to the above criteria |
| **VGPR (Very good partial response)** |
| Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR ≥ 90% reduction in serum M-protein plus urine M-protein level < 100mg/24h<br><br>In patients who lack measurable M-proteins in the serum and urine being monitored using FLC levels, the definition of VGPR requires > 90% decrease in the difference between involved and uninvolved FLC levels |
| **PR (Partial response)** |
| ≥ 50% reduction of serum M-protein AND reduction in 24h urinary M-protein by ≥ 90% or to < 200mg per 24h AND ≥ 50% reduction in size of any soft tissue plasmacytomas, if present at baseline<br><br>In patients who lack measurable M-proteins in the serum and urine being monitored using FLC levels, the definition of PR requires ≥ 50% decrease in the difference between involved and uninvolved FLC levels. If the FLC levels were also unmeasurable at baseline, a 50% reduction in bone marrow plasma cells is acceptable as long as the original BM contained ≥ 30% PCs. |
| **SD (Stable disease)** |
| Not meeting criteria for CR, VGPR, PR or PD |
| **PD (Progressive disease)** |
| Increase of ≥ 25% from baseline in any of the following: 1) serum M-protein (the absolute increase must be ≥ 0.5 g/dL), 2) urine M-protein (the absolute increase must be ≥ 200 mg/24h), 3) bone marrow plasma cell percentage (absolute increase must be > 10%), 4) difference in the kappa and lambda FLC (absolute increase must be > 10 mg/dL; this criteria should only be used for patients with unmeasurable M-protein in the serum or urine) OR increase in the size or development of new bone lesions or soft tissue plasmacytomas OR development of a serum calcium > 11.5 mg/dL without other cause |

## 14.4. Appendix 4. Dose Diary

| **Drug name: IBRUTINIB** | | | |
|---|---|---|---|
| How much: | How often: ONCE EACH DAY | | |
| MD: | | Phone: | |
| RN/Research coordinator: | | Phone: | |
| | | | |
| CYCLE #: | | | |
| | | | |
| Day | Date | Time | Comments |
| 1 | | : AM / PM | |
| 2 | | : AM / PM | |
| 3 | | : AM / PM | |
| 4 | | : AM / PM | |
| 5 | | : AM / PM | |
| 6 | | : AM / PM | |
| 7 | | : AM / PM | |
| 8 | | : AM / PM | |
| 9 | | : AM / PM | |
| 10 | | : AM / PM | |
| 11 | | : AM / PM | |
| 12 | | : AM / PM | |
| 13 | | : AM / PM | |
| 14 | | : AM / PM | |
| 15 | | : AM / PM | |
| 16 | | : AM / PM | |
| 17 | | : AM / PM | |
| 18 | | : AM / PM | |
| 19 | | : AM / PM | |
| 20 | | : AM / PM | |
| 21 | | : AM / PM | |
| 22 | | : AM / PM | |
| 23 | | : AM / PM | |
| 24 | | : AM / PM | |
| 25 | | : AM / PM | |
| 26 | | : AM / PM | |
| 27 | | : AM / PM | |
| 28 | | : AM / PM | |

## 14.5. Appendix 5. Child-Pugh Score

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

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

Source:

1. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . "Transection of te oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 1973;60: 646-9.

## 14.6. Appendix 6. ECOG Performance Status

| Status | Eastern Cooperative Oncology Group (ECOG) Performance Status[45] |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work. |
| 2 | Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

## 14.7. Appendix 7. Image Assessment of Bone Lesions

# Appendix 7. Image Assessment of Bone Lesions

| | POSITIVE | NEGATIVE |
|---|---|---|
| PET | • Increased focal FDG uptake within at least one bone corresponding to a lytic lesion more intense compared with liver uptake<br><br>• Increased focal uptake within at least one bone with no corresponding lytic lesion more intense compared with the adjacent bone uptake (outside the areas of prior intervention, compression, and degenerative changes)<br><br>• Diffuse BM involvement defined as a homogeneous uptake in the axial and appendicular skeleton >> liver uptake (SUVmax 2-3x ≥liver SUVmax) or significantly heterogeneous uptake < 2x liver SUVmax<br><br>• Extramedullary disease: FDG-avid soft tissue mass outside bony structures (not originating from bones) | • Any finding that does not fall into one of the described categories as outlined in the "positive" finding description<br><br>• All findings that correspond with benign osteoarthritic changes or recent interventions or previous trauma |
| PET/MR | • Hypointense T1, Hyperintense STIR<br>• Hyperintense DWI<br>• Hypointense ADC | • Hyperintense T1 Hypointense STIR<br>• Hypointense DWI<br>• Hyperintense ADC |

- **PET portion of PET/MRI will be interpreted by a nuclear medicine physcian and MRI by a diagnostic radiologist**
- **PET will be interpreted using the above criteria and quantitative analysis may be performed as a secondary step but the clinical read will rely on qualitative reading**
- **Interpretation of both parts of the integrated PET/MRI will not be blinded. Both PET and MRI interpreter will have an access to each others' reading. In cases where there is incongruency between readings a consensus will be reached by the two imagers**