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Phase I/II Trial of Ibrutinib, Dexamethasone, and Lenalidomide as Initial Therapy for Transplant Ineligible Multiple Myeloma Patients

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Mayo Clinic Cancer Center

Phase I/II Trial of Ibrutinib, Dexamethasone, and Lenalidomide as Initial Therapy for Transplant Ineligible Multiple Myeloma Patients

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Drug Availability
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Drug Company Supplied: Ibrutinib IND#132492

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Amendment 4	Pending Approval

Protocol Resources

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*No waivers of eligibility

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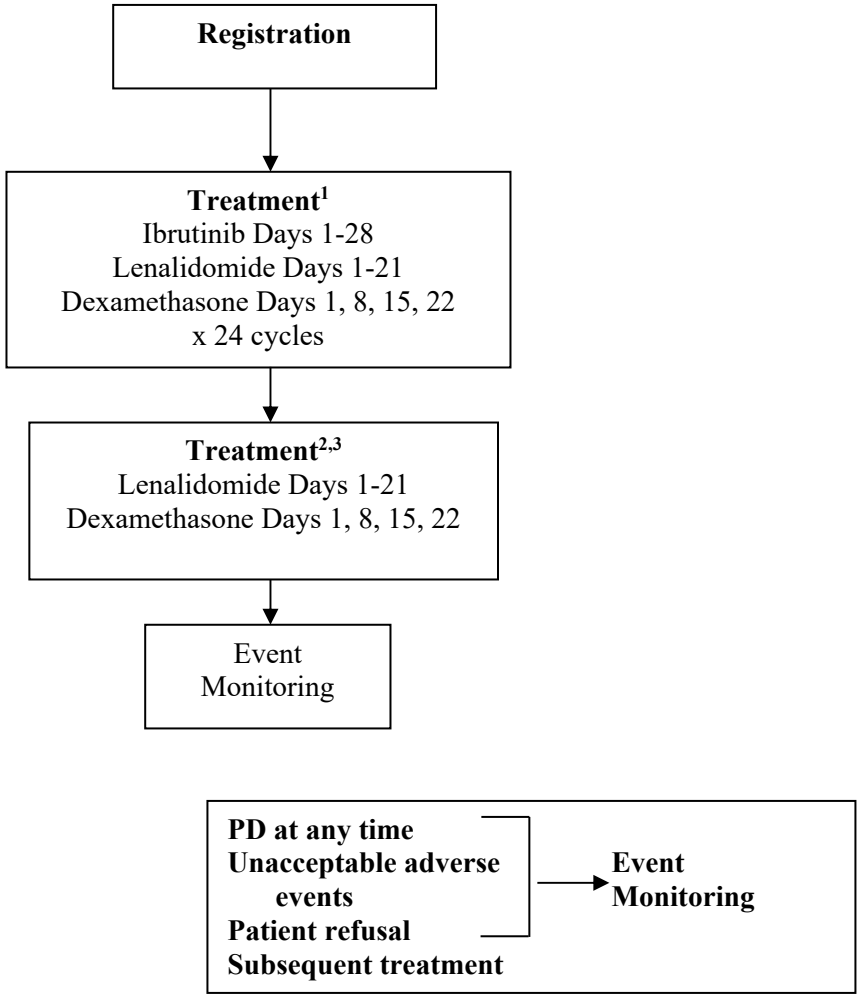
Schema – Phase 1 (1-3 prior lines of therapy)

Phase I only: Prior to discussing protocol entry with the patient, call the MCCC Registration Office (507-284-2753) for dose level and to insure that a place on the protocol is open to the patient.

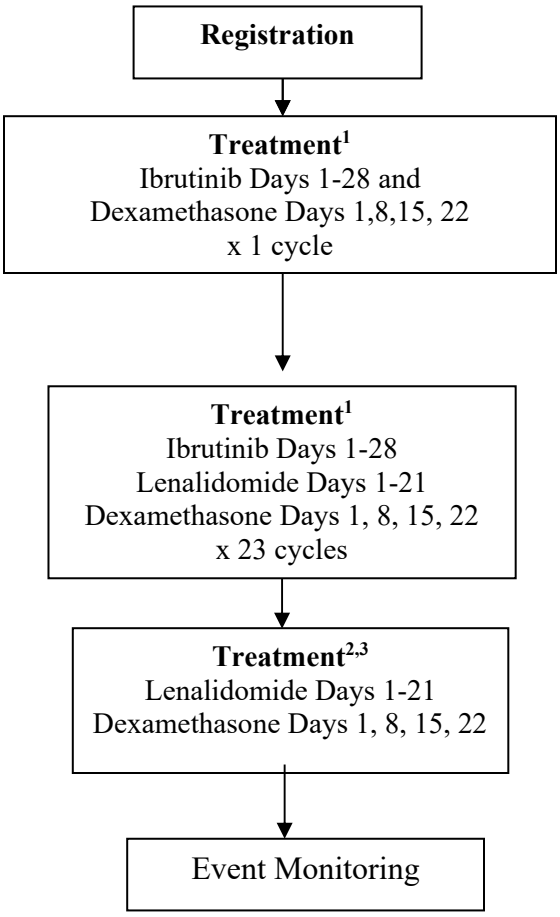


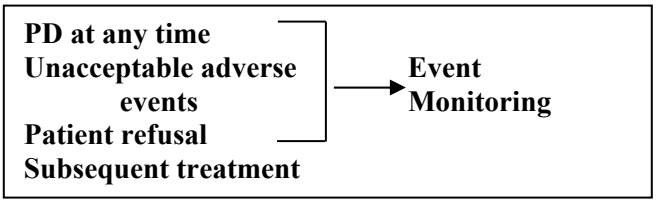
[1] Cycle length=28 days
[2] Cycle length = 84 days
[3] Repeat every 28 days x 3 for each cycle

Generic name: Ibrutinib Brand name(s): Imbruvica® Mayo Abbreviation: PCI-32765 Availability: Provided by Pharmacyclics	Generic name: Lenalidomide Brand name(s): Revlimid® Mayo Abbreviation: REVLIMID Availability: Commercial	Generic name: Dexamethasone Brand name(s): Decadron® Mayo Abbreviation: DXM Availability: Commercial

Schema – Phase II (previously untreated multiple myeloma)

NOTE: Phase II will not be initiated until after FDA review of Phase I data and approval to continue





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1.0 Background

1.1 Multiple Myeloma

Multiple myeloma is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The disease leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, neurological complications and hyper viscosity syndrome.

The majority of patients with multiple myeloma produce a monoclonal protein, also called paraprotein, M-protein or M-component, which is an immunoglobulin (Ig) or a fragment of one that has lost its function[1,2]. Normal immunoglobulin levels are compromised, leading to susceptibility of infections. The proliferating multiple myeloma cells displace the normal bone marrow leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, which is reflected by clinical findings such as anemia, paraprotein in serum or urine, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs [3]. Furthermore, hypercalcemia, renal insufficiency or failure, and neurological complications are frequently seen[4]. A small minority of patients with multiple myeloma are non-secretory.

At the time of diagnosis, multiple myeloma is a heterogeneous disease, with a course that varies on the basis of both disease- and host-related factors (e.g., age, renal function, stage, chromosomal abnormalities). Multiple myeloma causes significant morbidity and mortality. It accounts for approximately 1% of all malignancies and 13% of hematologic cancers. Approximately 50,000 patients per year are diagnosed with multiple myeloma in the EU and US, and 30,000 patients per year die due to multiple myeloma.

1.2 Treatment for Multiple Myeloma

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors[4]. Newly diagnosed patients with multiple myeloma are typically categorized into 2 subpopulations usually defined by their age and suitability for the subsequent approach to treatment. Younger patients will typically receive an induction regimen followed by consolidation treatment with high-dose chemotherapy and autologous stem cell transplantation (ASCT). For those not considered suitable for high-dose chemotherapy and ASCT, longer-term treatment with multi-agent combinations including alkylators, high-dose steroids, and novel agents are currently considered as standards of care.

Over the past few years several novel treatments (immunomodulatory drugs; IMiDs and proteasome inhibitors) have become available for patients with MM. Although higher percentages of patients are achieving remission, all patients eventually relapse and become resistant to therapy. Novel agents and new combinations regimens are needed for improved outcome in this disease. There is an increasing body of evidence suggesting that clinical or laboratory parameters may be important in selecting specific treatment options for patients with MM[5-7]. This is further important since the novel agents being used for the treatment of MM have their own inherent side effect profiles that are unique and need specific management as against the more expected adverse events from conventional chemotherapeutic agents. This is especially true in elderly patients who may

have other comorbidities, since the median age at diagnosis for MM is 70 years. Thus, there is a constant need to develop newer, better tolerated agents/regimens that can keep the disease controlled for prolonged durations as well as be safe with respect to low cumulative toxicities. A recently developed tool based on geriatric assessment has been validated in a pooled analysis by the International Myeloma Working Group and is recommended to be used prospectively in trials focusing on non-transplant eligible newly diagnosed MM patients, which is the target population for this proposed clinical trial.[8] This tool will be utilized in the said protocol to address patient eligibility.

1.3 Lenalidomide (len) and Dexamethsone (dex) in Treatment Naive MM Patients

The combination of len and dex is widely used as an initial regimen for elderly patients and those considered ineligible for ASCT)[9]. Although IMiDs are a relatively safe and convenient oral option for MM patients, they have their own set of adverse events including cytopenias, risk of thrombosis, necessitating the use of thromboprophylaxis, and more recently noted potential risk of second primary malignancies (SPM). Furthermore, len use in patients with renal insufficiency (seen in up to 20% patients with MM at the time of initial diagnosis) is difficult due to an amplified adverse event profile seen as a result of prolonged half-life of the drug in these patients. Newer agents that may be oral and free of such potential adverse events need to be tested in this MM population, where ASCT may not be an option due to age and comorbidities.

1.4 BTK Inhibition

One such novel agent is ibrutinib (ibr), a small-molecular inhibitor of Bruton's Tyrosine Kinase (BTK), administered by mouth once daily. In normal B-cell development the receptor for B-cell activating factor (BAFF) of the TNF family (BAFF-R) is coupled to the NF-κB pathway by BTK[10]. Loss of BTK results in defective BAFF-mediated activation of both canonical and non-canonical NF-κB pathways. Thus, BAFF-induced signaling to NF-κB via BTK serves to promote B-cell survival. These findings are in keeping with the clinical observations that genetic defects in BTK are associated with a profound deficiency of B-cells,[11] and that the BTK inhibitor ibr is cytotoxic to chronic lymphocytic leukemia (CLL) cells [12,13]. As the NF-κB pathway is central to myeloma cell survival, and BTK couples cell survival surface signals to the NF-κB pathway in B-cell development, as well as the BTK inhibitor, ibr being highly effective in killing CLL cells, further investigation of the efficacy of ibr in MM is warranted.

1.5 BTK Inhibition in B-cell Malignancies Including MM

Ibrutinib is approved by the FDA for the treatment of certain B-cell malignancies including CLL, Waldenstrom's macroglobulinemia (WM) and relapsed/refractory mantle cell lymphoma (MCL). Ongoing clinical trials are exploring the efficacy of ibrutinib, alone or in combination regimens in patients with MM. One of these, an open label phase 2 dose escalation study in patients with relapsed and/or refractory MM (n=69) with a median of 4 prior lines of therapy has shown that at Ibr doses higher than those used in CLL and MCL (840 mg vs. 420 mg and 560 mg, respectively), the clinical benefit rate (≥minor response) was 25% and another 25% achieved stable disease (SD), leading to a median progression free survival (PFS) of 5.6 months.[14] Patients in this clinical trial were relatively heavily pre-treated with median 4 prior lines of therapy. Another phase 1 clinical trial of Ibr (560-840 mg) in combination with carfilzomib (20/27-20/36 mg/m^2) and dexamethasone is underway and preliminary results have shown that at these doses

and in this combination, Ibr did not cause any dose-limiting toxicities (DLT) and the dose escalation is currently underway. Patients (n=39) in this trial had a median of 3 prior lines of therapy and all were refractory to their most recent therapy (presented at American Society of Hematology Annual Meeting, 2015). The overall response rate (ORR) noted was 58% with a clinical benefit rate of 67%. Of note, 25% of the patients enrolled had previous exposure to carfilzomib and pomalidomide. Other clinical trials of Ibr with anti-MM agents including pomalidomide are planned. Using it earlier on in the clinical course of MM patients may show a clearer signal of the efficacy of ibr in MM. Furthermore, long-term follow up data from patients treated with ibr for CLL, MCL and Waldenstrom's macroglobulinemia (WM) have shown an excellent tolerability of ibr, without any major or cumulative adverse events.

1.6 Rationale for Combining Ibrutinib with Lenalidomide

The exact mechanism of action for len is not fully understood. Efficacy of len is in part by augmenting interferon-β (IFNβ) production. In a cereblon-dependent fashion, len down regulates IRF4 and SPIB, transcription factors that together prevent IFNβ production by repressing IRF7 and amplify prosurvival NF-κB signaling by transactivating CARD11. Blockade of B cell receptor signaling by BTK inhibition using ibr also down regulates IRF4 and consequently synergizes with len in cell death, suggesting attractive combination therapeutic strategies[15]. Furthermore, we have performed apoptosis assays in resistant (CD20-) and sensitive (CD20+) WM (a plasma cell disorder related to MM) cell lines (BCWM1 and RPCIWM1), showing potential synergy for the combination of ibr and len (Figure 1; unpublished data). Two ongoing phase 1 trials of the combination of ibr and len in B-cell malignancies have recently been presented with initial reports. These include one in relapsed and/or refractory CLL[16], and the other in relapsed and/or refractory NHL[17]. Both these trials are currently undergoing dose escalations but are different from the proposed trial in MM since the patients in these trials were relatively heavily pre-treated. Since the dose of this combination, especially with dexamethasone which is an integral part of MM treatment is not yet determined, a formal phase 1 component of the trial is proposed and necessary.

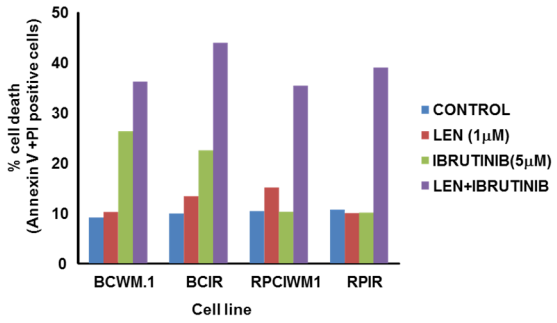

Figure 1. *In vitro* data showing potential synergy of Len+Ibr in MM and WM cell lines

Thus, it is rational to test the efficacy of ibr in MM as a single-agent as well as in combination with len+dex, especially in treatment-naive elderly or transplant ineligible patients, where a more favorable adverse event profile is desirable. Since such a combination has not been previously tested in MM, an initial phase 1 trial component with a recommended phase 2 dose (RP2D) strategy for the combination of ibr with len and dex is being proposed. After the RP2D of this combination has been determined, subsequent enrollment would be with patients initially treated with ibr and dex and after completing the first cycle of treatment with this (1 cycle=28days), len will be added. This will help provide important correlative data to explore the biological activity as well as pharmacodynamics of ibrutinib in myeloma, for which concrete data is so far lacking despite clinical trials showing efficacy.

1.7 Correlative Research

1.71 *To determine the role of members of the BTK signalosome in achievement or lack thereof of response to ibrutinib:* The variability in extent of response to a therapeutic agent may suggest underlying adaptability of the MM clone through components of the BTK signalosome. Patients with B-cell malignancies treated with ibr demonstrate upregulation of p-Akt and p-Erk (downstream mediators of BTK) in some (but not all) cases, suggesting that these pathways may contribute to survival of the malignant clone.[18] It was also concluded in this work that these cells might not be dependent upon the proximal BTK pathways mediated apoptosis and thus, resistant to killing by ibr. To address this question we will establish the profile of BTK signalosome for each patient through determination of the mRNA (RT-PCR/nanostring assay; whole exome sequencing (WES), transcriptom analysis) and protein expression (western blot analysis) of members of the BTK signaling pathway and look for associations between this and eventual response (or lack thereof) to the treatment. The said tests will be done analyzing the CD138+ cells enriched from the bone marrow samples collected at baseline, after 1 month of treatment with ibr alone and then at the time of disease progression. This will help explore mechanisms of acquired resistance to ibr. In MM. We will also look for pAKT, pS6 and pERK as indirect pharmacodynamic biomarkers analyzed in patient's PBMC collected as a peripheral blood sample at baseline and then after 1 cycle of treatment with ibr, prior to adding the len/ dex.

1.72 *To explore biologic effects of ibrutinib on microenvironment in MM and correlate with response to treatment:* In cancer redirection of host immunity from a predominant Th2 to Th1 response can deliver antitumor response. Ibr can bind to ITK, a member of the TEC-kinase family, which mediates TCR signaling through PLCg, NFAT, NF-kappaB and MAPK.[19] This results in activation and proliferation of CD8+ cells. Our hypothesis is that ibr alters the Th2:Th1 balance in the blood and bone marrow microenvironment, skewing towards a more Th1 profile and this may translate into its clinical efficacy. We further hypothesize that the robustness of the Th1 response will direct ibr's depth of response. We will assess this in bone marrow samples comparing the baseline sample to one collected after 1 cycle of treatment with ibr using the MultiOmyx Tumor Infiltrating Lymphocytes panel for T helper (CD4+), Treg (FOXP3+), T cytotoxic (CD8+), B cells (CD20+), macrophage (CD68+), NK cells (CD56+), immunosuppression (PD-L1), CD138+, CD38+, ITK and BTK. Furthermore, BTK/ITK occupancy by ibr has been associated with response rates in other B-cell malignancies where this is an effective agent (CLL) but this has never been tested in MM. This assay will be performed to assess target coverage in bone marrow samples obtained from patients at the end of 1 cycle of treatment with ibr. In addition, PBMC samples (2 ml of whole blood with heparin) from baseline and after 1 cycle of treatment with ibr will be assessed for:

Th1 cells (live+, CD19-, CD3+, CD4+, CD8-, IFNg+)
Th2 cells (live+, CD19-, CD3+, CD4+, CD8-, IL4+)
Th17 cells (live+, CD19-, CD3+, CD4+, CD8-, IL17+)
Treg cells (live+, CD19-, CD14-, CD3+, CD4+, CD25+, CD127-, FOXP3, CCR4+)

1.73 *To explore compliance to treatment:* The proposed regimen in this clinical trial is all-oral. Data from other malignant and non-malignant diagnoses (e.g., CML,

hypertension) where oral therapeutic agents are utilized have shown that patient adherence to treatment is significantly associated with a likelihood of achieving better disease control.[20-22] This has not been established yet in MM, where oral therapeutic agents are being used increasingly, especially in elderly patients where there may be a higher medication-burden. Patient compliance to ibr with len+dex will be assessed by means of self-reported and healthcare staff assessed pill count/diary. Correlation between medication adherence and disease response will be assessed.

1.74 *To assess effects of treatment on patient reported Quality of Life (QoL) measures:* Although orally available therapeutic agents may be more convenient, majority of them have to be taken on an ongoing basis as long as there is disease response and no "unacceptable" toxicities. This concept with long duration of therapy as well as the symptom complex from the disease and the therapeutic agents can significantly affect the patient's QoL, especially in patients with advanced age at the time of MM diagnosis.[23] In the proposed trial, patient-reported QoL will be measured with the MD Anderson Symptom Inventory – Multiple Myeloma (MDASI-MM), which has been a validated tool.[24] The MDASI-MM consists of 13 core items, 7 MM-specific symptom severity items and 6 interference items; the time frame for addressing symptom severity and interference is the last 24 hours. From these items, mean subscale scores have been derived: mean Core (13 core items), mean Severity (13 core items + 7 MM-specific items), and mean Interference (6 interference items); an exploratory analysis in this study will examine a 4th score, the mean Severity score for the 7 MM symptoms. Response options range from 0 ("not present") to 10 ("as bad as you can imagine") for the severity items and from 0 ("did not interfere") to 10 ("interfered completely") for the interference items. These will be completed by patients in a paper or electronic entry as per the following schedule:

- At baseline (within 14 days prior to starting treatment)
- At the end of 1 cycle of treatment
- At six months
- At one year of treatment
- At any time the patient is removed from the study protocol (due to disease progression or adverse events; within 14 days of removal from the study)

The primary outcome of interest for this trial is the difference in the change of the mean Symptom Severity score for the Core plus 7 MM symptom items from baseline to various time points noted above with this treatment regimen.

1.75 *To assess effects of treatment on bone turnover:* Bone turnover can be assessed by measuring serum levels of RNAKL, RNAK, NFκB, BAP, RUNX2, CBfa1, OPG, DKK1, MMP1, MMP2, sFRP-2 protein biomarkers. These will be checked at baseline and after 1 month of treatment with ibr alone in order to assess whether ibr suppresses osteoclast activation since bone resorption activity is an independent risk factor for overall survival in MM.

1.8 Trial Design

This will be a phase I/II non-randomized, open label, prospective clinical trial in patients with treatment naïve MM, who are considered ineligible for or otherwise refuse to undergo an ASCT. Since so far there have not been any clinical trials to determine the recommended dose of the combination of ibr with len and dex in MM, a phase I trial of this combination in patients with relapsed MM is planned. The reason to limit this trial to patients with relapsed MM is to establish safety as well as get an initial signal of efficacy of this combination in MM patients prior to introducing this in patients with newly diagnosed MM, where the proposed regimen of ibr+len+dex has never been studied before. Furthermore, the signal of efficacy in patients with relapsed disease would provide a more compelling justification to explore BTK inhibition in patients with newly diagnosed MM. In the phase I portion, the dose of len and dex would be fixed at the standard dose and the ibr dose would be adjusted to find the RP2D of this combination regimen.

1.9 Ibrutinib Summary of Clinical Safety

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies, which included 1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423):

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

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

1.91 Ibrutinib: Risks

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 15.20 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements and ibrutinib management with surgeries or procedures.

1.92 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 8).

1.93 Cytopenias

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

1.94 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 8).

1.95 Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0). 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.

1.96 Non-melanoma skin cancer

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

1.97 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.

1.98 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 LDH, bulky disease at baseline, and pre-existing kidney abnormalities**.**

1.99 Interstitial Lund 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 8).

2.0 Goals

2.1 Primary Objective:

2.11 Phase 1: To determine the maximum tolerated dose (MTD) of ibrutinib that can be combined with lenalidomide and dexamethasone in relapsed MM patients.

2.12 Phase 2: To estimate the overall response rate (ORR) including partial response (PR) or better of the combination of ibrutinib, lenalidomide, and dexamethasone in subjects with newly diagnosed MM who are not candidates for high dose chemotherapy and ASCT.

2.2 Secondary Objectives:

Phase I

2.21 To evaluate the safety profile of this regimen in relapsed MM patients.

Phase II

2.22 To evaluate the progression free survival (PFS) of the combination of ibrutinib, lenalidomide, and dexamethasone in MM patients

2.23 To evaluate the safety profile of this regimen in untreated MM patients.

2.24 To evaluate the duration of response for patients treated with this 3-drug regimen.

2.25 To evaluate overall survival (OS) for patients treated with this 3-drug regimen

2.3 Exploratory Objective:

2.31 To explore compliance to treatment.

2.32 To assess effects of treatment on patient-reported quality of life (QoL) measures

2.4 Correlative Research Objective:

2.41 To determine the role of members of the BTK signalosome in achievement or lack thereof of response to ibrutinib.

2.42 To explore biologic effects of ibrutinib on microenvironment in MM and correlate with response to treatment.

2.43 To evaluate pharmacodynamic measures including receptor occupancy for BTK prior to introducing lenalidomide in patients treated with ibrutinib and dexamethasone.

2.44 To evaluate the impact of ibrutinib on platelet aggregation.

3.0 Patient Eligibility

<u>Phase I only</u>: Prior to discussing protocol entry with the patient, call the MCCC Registration Office (507-284-2753) for dose level and to insure that a place on the protocol is open to the patient.

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Diagnosis:

3.121 Phase I: Confirmed diagnosis of relapsed or refractory multiple myeloma

3.122 Phase II: Confirmed diagnosis of active multiple myeloma and must be newly diagnosed.
NOTE: All tests for establishing disease status must be completed ≤28 days prior to registration.

3.13 Measurable disease ≤28 days prior to registration, defined by at least one of the following:

- Serum monoclonal protein ≥1.0 g/dL (see Section 11.1 for definition)
- >200 mg of monoclonal protein in the urine on 24-hour electrophoresis
- Serum immunoglobulin free light chain >10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.
- Monoclonal bone marrow plasmacytosis >30% (evaluable disease).

3.14 Prior treatment:

3.141 Phase I: Exposure to 2-3 prior lines of therapy or no therapeutic options

3.142 Phase II: Previously untreated for symptomatic MM.

EXCEPTION: ≤7 days with pulse steroids or localized radiation therapy, without curative intent, for a myeloma-related complication prior to registration is allowed, as considered necessary by the treating physician.

3.15 Myeloma Frailty Score:
NOTE: This will include calculating a frailty score [Appendix I; based on age, activities of daily living, instrumental activities of daily living (Appendix II) and Charlson comorbidity index (Appendix III)].

3.151 Phase I: "Intermediate fitness" or "Frail"
NOTE: No "fit" patients will be included in the phase 1 portion of the trial which is being done to determine the MTD of the 3-drug combination.

3.152 Phase II: Transplant-ineligible as per their treating physician.
NOTE: All the patients with "intermediate fitness" or "frail" status will be considered transplant-ineligible. Other reasons to consider transplant ineligibility may include, but are not limited to: financial constraints or patient preference. In case such patients have a frailty score of "fit", it should be duly noted by the treating physician.

3.16 ECOG Performance Status 0, 1, or 2 (Appendix IV).

3.17 The following laboratory values obtained ≤14 days prior to registration:
- Absolute neutrophil count (ANC) ≥1,000 cell/mm3 without growth factor support
- Platelets ≥50,000 cells/mm^3 for patients who have bone marrow plasmacytosis <50% or ≥30,000 cells/mm^3 for patients who have bone marrow plasmacytosis of ≥50%
- Calculated or measured creatinine clearance ≥30 ml/min (see Appendix V)
- Total bilirubin ≤1.5 x upper limit of normal (ULN) unless due to Gilbert's syndrome.
- Aspartate aminotransferase (AST)/SGOT and alanine aminotransferase (ALT)/SGPT ≤3 x ULN
- PT/INR ≤1.5 X ULN

3.18 Provide informed written consent.

3.19a Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19b Persons able to become pregnant must be willing to adhere to the scheduled pregnancy testing as required in the REVLIMID REMS™ program.

3.19c Willing to be registered into the mandatory REVLIMID REMS™ program, and willing and able to comply with the requirements of the REVLIMID REMS™ program.

3.19d Ability to complete study-related (QoL, pill diary) questionnaire(s) by themselves or with assistance.

3.19e Willing to provide bone marrow aspirate and core, and blood samples for correlative research purposes (see Sections 6.31, 14.0).

3.2 Exclusion Criteria

3.21 Non-secretory MM or known AL amyloidosis.

3.22 Clinically significant active infection requiring intravenous antibiotics ≤14 days prior to registration.

3.23 ≥Grade 3 neuropathy and/or POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

3.24 Other prior malignancy.
EXCEPTIONS:
- Adequately treated basal cell or squamous cell skin cancer
- Any *in situ* cancer
- Adequately treated Stage I or II cancer from which the patient is currently in complete remission, or
- Any other cancer from which the patient has been disease-free for ≥at least three years prior to registration

3.25 Concurrent therapy considered to be investigational.
NOTE: Patients must not be planning to receive any radiation therapy (except localized radiation for palliative care that must be completed prior to starting Cycle 1, Day 1).

3.26 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
- Nursing women (lactating females are eligible provided that they agree not to breast feed while taking lenalidomide)
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.27 Requires treatment with a strong cytochrome (CYP) 3A4/5 inhibitor (as outlined in Appendix X).

3.28 Major surgery ≤4 weeks prior to registration.

3.29a History of stroke/intracranial hemorrhage ≤6 months prior to registration.

3.29b Requires use of therapeutic anticoagulation prior to registration

NOTE: thromboprophylaxis with any agent is permitted.

3.29c History of clinically significant bleeding or known platelet or coagulation disorder.

3.29d Clinically significant cardiac illness including New York Heart Association (NYHA) Class III or Class IV heart failure (Appendix VI), unstable angina pectoris, myocardial infarction within the past 6 months, or ≥Grade 3 cardiac arrhythmias noted ≤14 days prior to registration.

3.29e Hepatic impairment

3.29e1 Phase I
Any currently active, clinically significant hepatic impairment (Child-Pugh class A, B, or C according to the Child Pugh classification see Appendix XII).

3.29e2 Phase II
Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix XII).

3.29f Known HIV+ patients
EXCEPTION: If they meet the following additional criteria ≤28 days prior to registration:
- CD4 cells ≥500/mm^3
- Viral load of <50 copies HIV mRNA/mm3 if on cART or <10,000 copies HIV mRNA if not on cART
- No zidovudine or stavudine as part of cART

3.29g Known Hepatitis B or Hepatitis C infection
EXCEPTION: If viral load <800,000 IU/L.

3.29h Phase I : Active dermatologic disease ≥ Grade 3.

4.0 Test Schedule

4.1 Test schedule Phase I and II

Tests and Procedures	Prior to Registration		Active Monitoring Phase			
	≤28 days prior to registration	≤14 days prior to registration	Every 14 days during 1st 2 cycles[a]	Cycles 1-24: Every 28 days (Day 1 of every cycle) pre-treatment[a,b]	Cycles 25 and after: Every 84 days (Day 1 of every cycle) pre-treatment[a,b]	End of treatment[a]
Informed Consent	X					
Complete medical and disease history		X	X	X	X	X
Physical examination including skin exam[c]		X	X	X	X	X
Height		X				
Vital signs[c]		X	X	X	X	X
Performance status (ECOG scale)(Appendix IV)		X		X	X	X
Registered in the REVLIMID REMS™ program[o]		X		X	X	
Hematology[d]		X	X	X	X	X
Coagulation[e]		X		X	X	
Blood chemistries[f]		X	X	X	X	X
Bone marrow aspirate and biopsy with standard clinical testing (including but not limited to myeloma FISH and flow cytometry)	X			X[g]	X[g]	X[g]
Electrophoresis of serum and urine (SPEP/UPEP)	X			X	X	X
Affected immunoglobulin	X			X[r]	X[r]	X[r]
Immunofixation serum and urine (IF)	X			X	X	X
Immunoglobulin free light chain (FLC)	X			X	X	X
Serum β2-microglobulin, CRP		X				
ECG[p]		X		X[p]	X[p]	
Skeletal bone survey	X			X[h]	X[h]	X[h]
PET scan	X			X[h]	X[h]	X[h]
Research blood sample (Section 14.0)[R]		X[q]		X	X	X
Research bone marrow (Section 14.0)[i,R]	X[q]			X	X	X
Concomitant medications[j]		X				
Adverse Event monitoring[k]		X	X	X	X	X
Pregnancy test[l]		X		X	X	X
Patient Medication Diary (Appendix VIII)[m]				X	X	X

Tests and Procedures	Prior to Registration		Active Monitoring Phase			
	≤28 days prior to registration	≤14 days prior to registration	Every 14 days during 1st 2 cycles[a]	Cycles 1-24: Every 28 days (Day 1 of every cycle) pre-treatment[a,b]	Cycles 25 and after: Every 84 days (Day 1 of every cycle) pre-treatment[a,b]	End of treatment[a]
Patient Questionnaire Booklets, (Appendix IX)[n]		X		X	X	X

Cycle length = 28 days Cycles 1-24; Cycle length = 84 days Cycles 25 and beyond

a) All scheduled visits will have a window of ±3 days unless otherwise stated, all procedures to be completed ≤3 days prior to commencing subsequent treatment cycle
b) Does not need to be repeated on Cycle 1, Day 1, if completed ≤14 days prior to registration
c) To include blood pressure, pulse rate, temperature, weight. Screening for second primary malignancies and especially dermatologic cancers is recommended per standard clinical practice. All patients must have documentation at baseline for any skin lesions considered at risk of a melanoma or non-melanomatous skin cancer. If any such lesion is identified, it should be addressed immediately. During the conduct of the clinical trial, please monitor for any potential skin malignancy lesions, as considered clinically necessary. All male patients at risk for prostate cancer recommended to undergo screening including a serum PSA level if not done ≤6 months prior to registration.
d) Hematology: CBC with differential, including hemoglobin and platelet count
e) Coagulation: prothrombin time (PT) and international normalized ratio (INR)
f) Blood chemistries: sodium, chloride, potassium, magnesium, phosphate, uric acid, BUN, glucose, ALT/AST (SGPT/SGOT), alkaline phosphatase, total protein, total bilirubin, albumin, serum creatinine, and estimated creatinine clearance (Appendix V), calcium and lactate dehydrogenase (LDH).
g) Standard of care procedure ≤28 days prior to registration, and to document CR, sCR or PD while on treatment (whether PD noted to single-agent ibr or the combination of ibr with len+dex). **NOTE:** For Phase II, an additional bone marrow biopsy and aspirate will be collected after completion of Cycle 1 of treatment for correlative sample collection in order to evaluate the exploratory endpoints of the study.
h) Skeletal bone survey and PET scan for extramedullary disease assessment ≤28 days prior to registration and then at any time when disease progression is noted, clinically or on laboratory assessment.
i) Per Section 14, to coincide with the timing of all standard-of-care bone marrow aspirate/biopsy collections in addition to a mandatory collection done prior to starting second cycle in Phase 2.
j) Concomitant medications: all on-going medications and those taken ≤14 days prior to first dose until 30 days after the last dose. Recorded in medical record only after baseline. Prior to every cycle, all patient medications must be reviewed and recorded in the medical record (see Appendix X for a list of contraindicated medications).
k) During treatment period, at end of treatment visit. The patient should be contacted by a nurse 30 days after the last dose of study treatment (or at the time of initiation of subsequent treatment if started before 30 days) to check if the patient has experienced any late adverse events. Grade 3 or higher adverse events at least possibly related to study treatment and deaths due to any cause should be reported as a late adverse event on the event monitoring form if they were not already reported on the Adverse Event form for the last cycle and they occurred prior to any subsequent treatment. and 30 days post-end of treatment

l) For persons of childbearing potential, a negative pregnancy test (urine or serum) must be documented. A person of childbearing potential is a sexually mature human with an intact uterus who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Frequency of testing as required by REMS® program or as clinically indicated.
m) To be collected on day 1 of every cycle starting cycle 2 and at end of treatment, in order to document patient compliance to treatment. Separate records to be collected for ibrutinib, lenalidomide and dexamethasone
n) MDASI-MM questionnaire to be completed at baseline (≤14 days prior to starting treatment), at the end of Cycle 1 (± 3 days), at the end of Cycle 6 (±3 days) and at completion of Cycle 12 of treatment (±3 days), at any time the patient progresses while on the 3-drug regimen and is removed from the study treatment (≤14 days after removal from the study)
o) All unused lenalidomide must be returned as instructed through the REVLIMID REMS™ program.
p) To be performed at screening and as clinically indicated throughout the study. Check ECG at any time if the patient's vital signs suggest an issue or if the patient has complaints that could be related to atrial fibrillation including subtle findings such as otherwise unexplained fatigue or nausea.
q) Collected after registration but prior to treatment.
r) Serum immunoglobulins to include IgA, IgG, IgM in all cases and IgD, IgE as clinically indicated.

R Research test (see Sections 14.0 and 19.0).

4.2 Event Monitoring/Survival Follow-up

	Event Monitoring Phase[1]				
	q. 3 months until PD or subsequent treatment	At PD or subsequent therapy	After PD or subsequent therapy q. 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.

5.0 Grouping Factor:

5.1 Phase I vs. Phase II

6.0 Registration/Randomization Procedures

6.1 Phase I

Prior to discussing protocol entry with the patient, call the MCCC Registration Office (507-284-2753) for dose level and to insure that a place on the protocol is open to the patient.

6.11 Registration Procedures

6.111 To register a patient, fax (507-284-0885) a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Phase II

6.21 Registration Procedures

6.211 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (http://ccswww.mayo.edu/training/) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office (507) 284-2753. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.3 Phase I and II

6.31 Correlative Research:
A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19e and 14.1).

6.32 Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution

- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.33 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.34 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of multiple myeloma at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.35 Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist/hematologist.

6.36 Treatment cannot begin prior to registration and must begin ≤ 28 days after registration.

6.37 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.38 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.39a Study drug is available on site.

6.39b Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

7.0 Protocol Treatment

7.1 Treatment Schedule

7.11 Phase I Treatment Schedule

Cycles 1-24

Agent	Dose Level	Route	Day	Cycles
Ibrutinib	As assigned by MCCC Registration Office	PO	1-28	Cycle 1-24
Lenalidomide	25 mg	PO	1-21	Cycle 1-24
Dexamethasone	40 mg*	PO	1, 8, 15, 22	Cycle 1-24

Cycle length = 28 days
*Starting dose level of dexamethasone for patients ≥75 years old will be 20mg

Cycles 25 and beyond

Agent	Dose Level	Route	Day		Cycles
Lenalidomide	25 mg	PO	1-21	Repeat every 28 days x 3 for each cycle	Cycles 25 and beyond
Dexamethasone	40 mg*	PO	1, 8, 15, 22		Cycles 25 and beyond

Cycle length = 84 days
*Starting dose level of dexamethasone for patients ≥75 years old will be 20mg

Treatment schedule will follow the study schema outlined above. All patients will start with ibrutinib as assigned by the registration office, lenalidomide 25 mg PO days 1-21, and dexamethasone 40 mg PO weekly. **EXCEPTION:** Lenalidomide will be adjusted per guidelines for renal dysfunction with CrCl between 30-60 ml/min (see Table 8.32).

Treatment will be continued until disease progression as long as the patient continues to respond and does not have any unacceptable toxicity. All the patients enrolled in the trial will have a follow up for at least 3 years after registration to capture the secondary endpoints of the study.

Note: Thromboprophylaxis is required as standard of care (see Section 9.3).

7.12 Phase II Treatment Schedule (To be implemented after FDA review of Phase I)

Cycles 1-24

Agent	Dose Level	Route	Day	Cycles
Ibrutinib	As determined in Phase I	PO	1-28	Cycle 1 and beyond
Lenalidomide	25 mg	PO	1-21	Cycle 2 and beyond (Not given in Cycle 1)
Dexamethasone	40 mg*	PO	1, 8, 15, 22	Cycle 1 and beyond

Cycle length = 28 days
*Starting dose level of dexamethasone for patients ≥75 years old will be 20mg

Cycles 25 and beyond

Agent	Dose Level	Route	Day		Cycles
Lenalidomide	25 mg	PO	1-21	**Repeat every 28 days x 3 for each cycle**	Cycles 25 and beyond
Dexamethasone	40 mg*	PO	1, 8, 15, 22		Cycles 25 and beyond

Cycle length = 84 days
*Starting dose level of dexamethasone for patients ≥75 years old will be 20mg

Treatment schedule will follow the study schema outlined above. All patients will start with ibrutinib at the dose level determined by the phase I portion and dexamethasone 40 mg PO weekly. Lenalidomide 25 mg PO Days 1-21 will be added Cycle 2.

Treatment will be continued until disease progression as long as the patient continues to respond and does not have any unacceptable toxicity. All the patients enrolled in the trial will have a follow up for at least 3 years after registration to capture the secondary endpoints of the study.

7.2 Treatment by a local medical doctor (LMD) is not allowed.

7.3 Phase I – determination of Maximum Tolerated Dose (MTD)

7.31 Dose Escalation (Phase I):

Dose level escalations/de-escalations will be done during the Phase I portion for Ibrutinib. In case any dose modifications to ibrutinib and/or dexamethasone are required during the Phase I portion due to specific adverse events requiring dose modifications (as outlined in Section 8 below), a specific discussion should be done with the study PI and appropriately documented. A patient on the Phase I portion of the study who develops a DLT should have treatment omitted until the toxicity resolves to Grade 1 or better or baseline, and then may be restarted at the next lower dose level for the DLT portion only. .

Only DLTs occurring in the first cycle and at the patient's first Dose Level of treatment will be used to guide dose determination for the Phase II portion of the trial per Section 16.22.

Dose level	Ibrutinib	Lenalidomide	Dexamethasone**
-1	280 mg	25 mg	40 mg
1*	420 mg	25 mg	40 mg
2	560 mg	25 mg	40 mg
3	700 mg	25 mg	40 mg
4	840 mg	25 mg	40 mg

*Starting dose level
**Starting dose level of dexamethasone for patients ≥75 years old will be 20mg

7.311 Three patients will be treated at each dose level and observed for a minimum of 28 days, to assess toxicities, before new patients are treated. Doses will not be escalated in any individual patient.

7.312 Investigators are to contact the Study Chair as soon as any dose-limiting toxicity (DLT) occurs.

7.32 **Definitions of DLT**: For this protocol, dose-limiting toxicity (DLT) will be defined as an adverse event attributed (definitely, probably, or possibly) in the first cycle to the study treatment and meeting the following criteria (as per CTCAE V4.0):

a) Any Grade 3 or greater non-hematological toxicity will be a DLT, with the exception of: fatigue, inadequately treated nausea, vomiting, or diarrhea; inadequately treated hyperglycemia; or hypersensitivity reaction. A rash considered associated with immune activation phenomenon secondary to

lenalidomide and/or ibrutinib will not be considered a DLT and may be treated concurrent to study treatment with solumedrol (Recommended treatment would be with a Medrol Dose Pak®)For a baseline abnormality prior to drug therapy, a worsening by at least 2 CTCAE grades and of clinical significance will be considered a DLT.

b) Grade 3 nausea, vomiting or diarrhea will be a DLT if it occurs despite appropriate maximal anti-emetic and/or antidiarrheal therapy.

c) Grade 3 hyperglycemia will be a DLT if the patient is symptomatic or glucose level is >300 mg/ml despite appropriate administration of insulin and/or oral antidiabetic agents.

d) Grade 4 neutrophil count decreased lasting >7 days or Grade 3 or 4 febrile neutropenia associated with fever (≥38.5℃).

e) Grade 4 platelet count decreased. Grade 3 platelet count decreased lasting >7 days or associated with Grade 2 or higher hemorrhage.

f) Delay of treatment with ANY agent for ≥14 days due to possibly, probably or definitely treatment-related toxicity during Cycle 1.

7.4 Overdose

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

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

Refer to Section 10 for further information regarding AE reporting.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first cycle of combination treatment with ibrutinib, lenalidomide and dexamethasone, until individual treatment tolerance can be ascertained (**not including the treatment period where MTD of the combination is being determined as per Section 7.31**). Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: ADR reporting may be required for some adverse events (See Section 10)

8.1 General Considerations:

a) Missed doses are to be omitted rather than made up, unless the dose of one of the study drugs was forgotten and remembered on the same day, in which case the dose can be taken that day. Any doses missed on a particular day are not to be made up the next day.

Doses that are considered to be vomited are not to be made up and a mention about the time of dose and time of vomiting episode should be made in the pill diary.

b) If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c) Reductions are based on the dose given in the preceding cycle and are based on toxicities with an attribution of possible, probable, or definite that were observed since the prior toxicity evaluation.

d) If either ibrutinib or lenalidomide must be permanently discontinued, the patient will be removed from the protocol therapy.

e) If a drug is omitted due to specific adverse events and the patient is on combination therapy, the other agents, considered unrelated to the adverse event may be continued.

f) A dose omission of >28 days for ibrutinib or lenalidomide is not allowed. If a patient cannot be administered a dose for >28 days due to adverse events or any other reason, the patient should be removed from the study treatment and go to event monitoring.

g) Patients will be removed from the study if we are unable to manage the adverse events they experience, and it is therefore necessary to permanently discontinue ibrutinib or lenalidomide. These events are listed in the tables in Section 8.3 and 8.5.

8.2 Dose Reductions for Phase I cycles 2 and beyond and Phase II portion (based on Adverse Events in Tables below):

8.21 The following recommended dose modifications will be utilized for ibrutinib, lenalidomide and/or dexamethasone separately as per the best judgment of which drug was most likely to have caused the toxicity:

8.22 Dose level tables

8.221 Lenalidomide

Dose Level	**Lenalidomide* Starting Dose 25 mg**
1st dose reduction	20 mg
2nd dose reduction	15 mg
3rd dose reduction	10 mg
4th dose reduction	Discontinue

*Other than lenalidomide dose adjusted for renal dysfunction

8.222 Dexamethasone

Dose Level	**Dexamethasone Starting Dose 40 mg***
1st dose reduction	20 mg
2nd dose reduction	12 mg
3rd dose reduction	8 mg
4th dose reduction	Discontinue

*Starting dose level of dexamethasone for patients ≥75 years old will be 20mg so those patients will start with the 2nd dose reduction row.

8.223 Ibrutinib

Ibrutinib	Starting Dose 840 mg	Starting Dose 700 mg	Starting Dose 560 mg	Starting Dose 420 mg	Starting Dose 280 mg
1st dose reduction	700 mg	560 mg	420 mg	280 mg	Discontinue
2nd dose reduction	560 mg	420 mg	280mg	Discontinue	
3rd dose reduction	420 mg	280mg	Discontinue		
4th dose reduction	280 mg	Discontinue			
5th dose reduction	Discontinue				

8.3 Lenalidomide Dose Modifications

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Investigations	Platelet count decreased Grade 4	Lenalidomide	*Omit dose until AE has resolved to Grade 1 or better • Follow CBC weekly • If thrombocytopenia <30,000/mm^3 recurs, reduce dose by one dose level (by 5 mg) and continue therapy when platelet count ≥30,000/mm^3 If, after lenalidomide has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient must be removed from protocol treatment and proceed to Event Monitoring
	Neutrophil count decreased Grade 4		*Omit dose until AE has resolved to Grade 1 or better • Follow CBC weekly * If neutropenia has resolved to ≤Grade 2, resume dose at one level lower *If, after lenalidomide has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient must be removed from protocol treatment and proceed to Event Monitoring

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Blood and lymphatic system disorders	Anemia Grade 4		*Omit dose until AE has resolved to Grade 2 or better • Follow CBC weekly * If anemia has resolved to ≤Grade 2, resume dose at one level lower *If, after lenalidomide has been omitted, and the AE does not return to ≤Grade 2 within 4 weeks, then the patient must be removed from protocol treatment and proceed to Event Monitoring
	Febrile neutropenia ≥Grade 3		• Omit dose and follow CBC weekly • If neutropenia has resolved to ≤Grade 2, resume dose at same level with GCSF support (See Section 9.7)
Cardiac disorders	Sinus bradycardia/ other cardiac arrhythmia Grade 2	Lenalidomide	Omit dose and follow at least weekly until resolution • If AE resolves to ≤Grade 1, reduce dose by one dose level (by 5mg) and continue therapy
	≥ Grade 3		• Discontinue study treatment and go to event monitoring
Vascular disorders	Thromboembolic event ≥ Grade 3		• Omit dose and start anticoagulation; restart at investigator's discretion (maintain dose level)
Immune system disorders	Allergic reaction Grade 2-3		• Omit dose and follow at least weekly until resolution • If AE resolves to ≤Grade 1, reduce dose by 5 mg and continue therapy
	Anaphylaxis Grade 4		• Discontinue study treatment and go to event monitoring
Skin and subcutaneous tissue disorders	Erythema multiforme ≥Grade 3		Discontinue study treatment and go to event monitoring
	Skin ulceration ≥Grade 2		Discontinue study treatment and go to event monitoring
	Other: Non-blistering rash Grade 3		• If Grade 3 omit dose and follow weekly until resolution • If AE resolves to ≤Grade 2 continue therapy
	Other: Non-blistering rash Grade 4		• Discontinue study treatment and go to event monitoring
Other AEs	Non-hematologic AE assessed as related to lenalidomide ≥Grade 3		• Omit dose and follow at least weekly until resolution • If the AE resolves to ≤Grade 2, implement one dose reduction step and continue therapy (per Table 8.2)

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm
** Use the following to describe actions in the Action column:
- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

If lenalidomide has been omitted and the toxicity does not return to ≤Grade 2 within 28 days, the patient must be removed from protocol treatment and proceed to Event Monitoring.

8.31 Lenalidomide dose adjustment for renal function

Lenalidomide dose will be adjusted as per standard of care guidelines in the prescribing information of lenalidomide for multiple myeloma patients. Patients with creatinine clearance (CrCl) <30 ml/min noted while on treatment and not considered secondary to disease progression will have dose modifications as per the following guidelines. Patients with baseline CrCl <30 ml/minute are not eligible for this study.

Table 8.32: Lenalidomide dose adjustment for baseline renal dysfunction

Creatinine Clearance (CrCl)	**Lenalidomide Dose**
CrCl >60 ml/minute	No adjustment required*
CrCl 30-60 ml/minute	10 mg once daily (may increase to 15 mg once daily after 2 cycles if nonresponsive but tolerating treatment)
CrCl <30 ml/minute (non-dialysis dependent)	15 mg every 48 hours

*The starting dose would be as determined by the phase 1 of the trial. MTD will be utilized for phase 2 as long as the CrCl >60 ml/minute and dose adjustments needed as per the table if CrCl <60 ml/minute.

8.4 Dexamethasone Dose Modifications

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Metabolism and nutrition disorders	Hyperglycemia (despite adequate anti-hyperglycemic management) Grade 2	Dexamethasone	Treatment with insulin or oral hypoglycemics as needed
	Grade 3 or 4		• Discontinue dexamethasone * Can continue lenalidomide and ibrutinib as per protocol

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Gastrointestinal disorders	Upper gastrointestinal hemorrhage Grade 3 or 4 OR Lower gastrointestinal hemorrhage Grade 3 or 4		• Discontinue dexamethasone * Can continue lenalidomide and ibrutinib as per protocol
	Pancreatitis ≥ Grade 3 (Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support))		Discontinue dexamethasone and do not resume * Can continue lenalidomide and ibrutinib as per protocol
Gastrointestinal disorders	Dyspepsia, gastric or duodenal ulcer, gastritis ≥Grade 3 (Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self-care ADL; disabling)	Dexamethasone	Omit dexamethasone until symptoms adequately controlled Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, discontinue dexamethasone and do not resume Can continue lenalidomide and ibrutinib per protocol
Cardiac Disorders	Sinus bradycardia/ other cardiac Arrhythmia Grade 3 or 4		Omit dose and follow at least weekly If the AE resolves to ≤Grade 2, implement one dose reduction step and continue therapy
General disorders and administration site conditions	Edema ≥Grade 3 (limiting function and unresponsive to therapy or anasarca)		Diuretics as needed, and decrease dexamethasone dose by 1 dose level If edema persists despite above measures, decrease dose another dose level Discontinue dexamethasone and do not resume if symptoms persist despite second reduction Ibrutinib and lenalidomide should be continued.
Psychiatric disorders	Confusion or Mood alteration ≥ Grade 2 (Severe disorientation; limiting selfcare ADL)		Omit dexamethasone until symptoms resolve Restart with one dose level reduction If symptoms persist despite above measures, discontinue dexamethasone and do not resume Ibrutinib and lenalidomide should be continued.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Other	Non-hematologic AE assessed as lenalidomide related ≥Grade 3		Omit dose and follow at least weekly If the AE resolves to ≤Grade 2, implement one dose reduction step and continue therapy

8.5 Ibrutinib Dose Modifications

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←

CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Investigations	Neutrophil count decreased Grade 4 lasting >7 days Platelet count decreased Grade ≥3	Ibrutinib	Omit ibrutinib** until recovery to Grade ≤1 or baseline May restart at same dose for first occurrence Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤1 or baseline If AE occurs at lowest dose discontinue treatment and go to event monitoring
Blood and lymphatic system disorders	Febrile neutropenia ≥Grade 3		Omit ibrutinib** until fever resolves and ANC ≥1000/μL, then resume ibrutinib at the previous dose
Gastrointestinal disorders	Nausea ≥Grade 3 (if persistent despite optimal antiemetic therapy) Vomiting ≥Grade 3 (if persistent despite optimal antiemetic therapy) Diarrhea ≥Grade 3 (if persistent despite optimal anti-diarrheal therapy)		Omit ibrutinib** until recovery to Grade ≤1 or baseline May restart at same dose for first occurrence Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤ 1 or baseline If AE occurs at lowest dose discontinue treatment and go to event monitoring
Other (Non-hematologic)****	Any other Grade 4 AE or any unmanageable Grade 3 AE		Omit ibrutinib** until recovery to Grade ≤1 or baseline May restart at same dose for first occurrence Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤1 or baseline If AE occurs at lowest dose discontinue treatment and go to event monitoring

Additional Adverse Events:

** If ibrutinib is omitted in the middle of the cycle and the toxicity resolves, patient can re-start the drug but the days of drug treatment missed do not need to be caught-up and can be omitted in order to maintain the cycle schedule.

- Dose omission: Ibrutinib may be omitted for adverse event considerations for a maximum of 28 consecutive days. Study medication should be discontinued permanently in the event of AE lasting more than 28 days.
- If multiple adverse events are seen, administer dose based on the greatest reduction required by any single adverse event observed.
- Dose modifications are for adverse events attributed to study treatment only. Dose modifications are not required for adverse events if they are deemed unrelated and/or unlikely related to study treatment.

- Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

**** If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO) should be considered. Consider Pneumocystis pneumonia or viral pneumonitis. Patients who experience a deep vein thrombosis (DVT), pulmonary embolus (PE), or other clotting event should have all study drugs temporarily omitted while full-dose anticoagulation is initiated (other than warfarin or other Vitamin K antagonist). There should not be a delay of more than 28 days in reinitiating the study treatment.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire remaining length of the study treatment.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) (per Table 8.2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

NOTE: For a dose omission of ibrutinib or lenalidomide of more than 28 days beyond the scheduled date of retreatment, the patient should discontinue protocol treatment and go to the event monitoring phase per Section 4.2. In the event patient is benefitting from treatment and the delay was unrelated to treatment toxicity, patient may remain on study with approval of study PI.

8.51 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 omit ibrutinib until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix XII).

9.0 Ancillary Treatment/Supportive Care

9.1 Full Supportive Care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Bisphosphonates

Patients may receive concurrent treatment with a bisphosphonate.

9.3 Thrombophylaxis

Due to the increased risk of deep vein thrombosis (DVT) for multiple myeloma patients, thromboprophylaxis is to be used as standard of care on this regimen according to the International Myeloma Working Group guidelines (http://jco.ascopubs.org/content/32/6/587.full).[26]

9.4 Steroids

Patients may continue on low level/stable steroid doses for replacement or inhalation therapy if they were on these prior to initiating the study treatment, provided that the chronic, stable steroid replacement dose is < 10 mg of prednisone daily or its equivalent.

9.5 Prohibited medications

The following medications are not permitted during the trial:

- Any other investigational treatment
- Any cytotoxic chemotherapy
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- Any external beam radiotherapy

9.6 Anti-emetics

Anti-emetics may be used at the discretion of the attending physician

9.7 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines.[27]

9.8 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.9a Concomitant medications

Any systemic, anti-myeloma therapy or steroids other than those prescribed by the protocol are prohibited while on protocol therapy. Guidelines for selection and use of other concomitant medications should be derived from the lenalidomide, ibrutinib and dexamethasone prescribing information. Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study (see Section 15.0 for a complete list).

9.9b Patients at high risk for tumor lysis syndrome

Patients considered by the treating physician to be at a high risk of tumor lysis syndrome should be started on appropriate tumor lysis prophylaxis such as allopurinol.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to CANCERCROSAFETYIN@mayo.edu

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

10.1 Adverse Event Characteristics

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

a. Identify the grade and severity of the event using the CTCAE version 4.0.

b. Determine whether the event is expected or unexpected (see Section 10.2).

c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

e. Determine if other reporting is required (see Section 10.5).

f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the <u>SAME</u> (Combination) Arm**

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.

- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent)

occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.

- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf
  or
  http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/default.htm

  Instructions for completing the MedWatch 3500A:
  http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*
*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
Gastrointestinal Disorders	Diarrhea	≤Grade 3
	Nausea	≤Grade 3
	Vomiting	≤Grade 4
General disorders and administration site conditions	Fatigue	≤Grade 4
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported[1]
	Platelet count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.
Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:
- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.]

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Submit the Medwatch form and the CIOMS 1 form via email AEintakeCT@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 Sponsor Investigator.

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the Reportable Event coversheet and appropriate documentation to CANCERCROSAFETYIN@mayo.edu. The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.

- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

  - Myelodysplastic syndrome (MDS)

  - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent

form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 **Baseline and Adverse Events Evaluations**
Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Anemia		X
Gastrointestinal disorders	# of stools	X	
	Diarrhea		X
	Nausea		X
General disorders and administration site conditions	Fatigue	X	X
Investigations	Neutrophil count decreased		X
	Platelet count decreased		X
Nervous system disorders	Peripheral motor neuropathy	X	X
	Peripheral sensory neuropathy	X	X

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Adverse Events of Special Interest (AESI)

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

10.81 Major Hemorrhage

Major hemorrhage is defined as any of the following:

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

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.0.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 10.8 above.

11.0 Treatment Evaluation

The International Myeloma Working Group (IMWG) uniform response criteria will be used to assess response to therapy.[28]

11.1 Terms and definitions

- **Monoclonal protein:** synonyms include M-spike, M-protein and myeloma protein, paraprotein, M-component.

  Serum Monoclonal protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.
  - Monoclonal protein migrating in the β-region (usually IgA Monoclonal protein)
  - Cases in which the Monoclonal protein is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
  - Cases in which there are multiple peaks of same Monoclonal protein (aggregates or dimers)

  If SPEP is not available or felt to be unreliable (above examples) for routine Monoclonal protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived Monoclonal protein values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

  Urine Monoclonal protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

FLC estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

  In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine Monoclonal proteinrotein.

  - Serum Monoclonal protein ≥1 g/dl
  - Urine Monoclonal protein ≥ 200 mg/24 h
  - Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal
  - Bone marrow plasma cells ≥ 30%

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. ***Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine Monoclonal protein) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results*** with the exception of defining stringent complete response.

- **Evaluable disease**: Patients who do not have a "measurable" serum Monoclonal protein, serum free light chain, or urine Monoclonal protein.

- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum Monoclonal protein or urine Monoclonal protein, but has had a detectable Monoclonal protein in his/her serum and/or urine and/or measurable serum free light chain.

- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable Monoclonal protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

Table 11.2

Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])

On Study Baseline Value	SPEP[4]	24 hr UPEP[2]	Ig FLC	BM Bx
Serum Monoclonal protein ≥1 g/dl, and urine Monoclonal protein ≥200 mg/24 hrs	X	X		
Serum Monoclonal protein ≥1 g/dl, but urine Monoclonal protein <200 mg/24 hrs	X			
Serum Monoclonal protein <1 g/dl, and urine Monoclonal protein ≥200 mg/24 hrs		X		
Serum Monoclonal protein <1 g/dl, urine Monoclonal protein <200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X	
Serum Monoclonal protein <1 g/dl, urine Monoclonal protein <200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow ≥30% plasma cells				X[3]

[1] **SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy** are required to document CR regardless of registration values, and in addition **FLC** measurement and **bone marrow immunophenotyping** is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.

[2] For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category

[3] At a minimum, a bone marrow biopsy should be repeated every 3 months until documented response. Bone marrow biopsy results do not need to be repeated after documented response.

[4] If serum Monoclonal proteinrotein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.

11.3 Confirmed response

In order to be classified as a hematologic response, confirmation of serum M- protein, serum immunoglobulin free light chain (when primary determinant of response) and urine M- protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case.
- Radiographic studies are not required to satisfy these response requirements;

however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.2

11.4 Bone progression

Caution must be exercised to avoid rating progression on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from the study.

11.5 Response and Progression

Criteria for response and progression are listed in Table 11.5. Progressive disease for all patients as defined in Table 11.5.

NOTE: For patients that have progressive disease on ibrutinib and dexamethasone during cycle 1, baseline values for the assessment of response to the combination of ibrutinib, dexamethasone, and lenalidomide will be defined as the values at the end of cycle 1.

Table 11.5

CATEGORY	RESPONSE CATEGORY [a]
Stringent Complete Response (sCR) [b]	• CR as defined *plus* • Normal FLC ratio *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4- color flow cytometry [i]
Complete Response (CR) [b]	• Negative immunofixation of serum and urine [c] *and* • Disappearance of any soft tissue plasmacytoma *and* • <5% PCs in Bone Marrow *and* • If the only measurable disease is FLC, a normal FLC ratio [d]
Very Good Partial Response (VGPR)	• Serum and urine Monoclonal protein detectable by immunofixation but not on electrophoresis [c] *or* • ≥90% reduction in serum Monoclonal protein and urine Monoclonal protein <100 mg/24 h [c] • If the only measurable disease is FLC, a >90% reduction in the difference between involved and uninvolved FLC levels
Partial Response (PR)	• If present at baseline, ≥50% reduction of serum Monoclonal protein and reduction in 24-hour urinary Monoclonal protein by ≥90% or to <200 mg/24hrs [c] • If the only measurable disease is FLC, a ≥50% reduction in the difference between involved and uninvolved FLC levels • If the only measurable disease is BM, a ≥50% reduction in BM PCs (provided the baseline PCs was ≥30%) • If present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas
Minor Response (MR)	• If present at baseline, ≥25% but ≤49% reduction of serum M protein *and* reduction in 24-hour urine Monoclonal protein by 50-89% which still exceeds 200mg/24 hours [c] *and* • If present at baseline, 25-49% reduction in the size of soft tissue plasmacytoma *and* • No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progressive Disease	Increase of 25% from lowest value in any of the following [f, g]:

Table 11.5	
CATEGORY	RESPONSE CATEGORY [a]
(PD) [b, h]	• Serum Monoclonal protein (absolute increase must be ≥ 0.5 g/dL) *and/or* • Urine Monoclonal protein (absolute increase must be ≥200 mg/24 hrs) *and/or* • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) *and/or* • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be ≥10%) [e] Or any one or more of the following: • Development of new bone lesion or soft tissue plasmacytoma or definite increase in the size of existing bone lesions or soft tissue plasmacytoma • Development of hypercalcemia (corrected serum calcium >11.5mg/dL) that can be attributed solely to the PC proliferative disorder
Stable Disease (SD)	Not meeting criteria for sCR, CR, VGPR, PR, MR or PD

[a] All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at any time before the institution of any new therapy; sCR, CR, VGPR, PR, MR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u"] to designate first time point at which response category MAY have been achieved if confirmed.

[b] CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient.

[c] If more than one M protein spike meets the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

[d] In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.

[e] Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC;

[f] A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum Monoclonal protein is ≥ 5 g/dL, an increase in serum Monoclonal protein of ≥ 1 g/dL is sufficient to define disease progression.

[g] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

[h] Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

[i] Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

12.0 Descriptive Factors

12.1 Parameters followed for hematologic response (pick one): serum monoclonal protein ≥1 g/dL and urine monoclonal protein ≥200 mg/24 hours vs. serum monoclonal protein ≥1g/dL only vs. urine monoclonal protein ≥200 mg/24 hours only vs. serum immunoglobulin free light chain ≥10 mg/dL with an abnormal free light chain ratio vs. bone marrow plasma cells >30%. Distinguish between SPEP measurements versus quantitative IgA measurements for serum monoclonal protein.

12.2 MM risk categories (As per Appendix VII): High vs. standard/intermediate

12.3 MM patient frailty patient status (per Appendix I): fit vs. intermediate fitness vs. frail

12.4 Phase I only: Dose Level (to be assigned by Registration Office):
-1 vs. 1 vs. 2 vs. 3 vs. 4

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are responding

Patients who are sCR, CR, VGPR, PR, MR, or SD (or usCR, uCR, uVGPR, uPR, uMR) will continue treatment per protocol. Treatment may continue until disease progression as long as the patient continues to respond and does not have any unacceptable toxicity.

13.3 Criteria for Initiation of Event Monitoring

Patients who go off protocol treatment for the following reasons will go to the event monitoring phase per Section 4.2:

- Progressive multiple myeloma while on combination treatment with ibrutinib, lenalidomide and dexamethasone
- Patient requests to discontinue study treatment
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Patient is lost to follow-up (defined as the inability to contact the patient for more than 2 years
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation
- A dose omission of more than 28 days beyond the scheduled date of retreatment for ibrutinib or lenalidomide

All attempts should be made to complete the End of Study procedures if a patient goes off treatment early.

13.4 Criteria for Study Discontinuation

The study may be temporarily or permanently discontinued at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice guidances or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

All Investigators and the requisite regulatory authorities will be notified if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB.

13.5 Failure to complete Cycle 1

Phase I Only: If a patient fails to complete the first cycle (each cycle=28 days) of the treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

13.6 Ineligibles

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.7 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 4.2 of the protocol.

13.8 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	Every cycle	End of treatment	Process at site?	Temperature Conditions for Storage /Shipping
BTK Signalosome	Mandatory	Bone marrow aspirate	Green Top tube	5 mL (2)	Baseline/ \after registration but prior to treatment	Prior to addition of len to ibr-dex* and as clinically indicated***	Confirmed disease progression	No	On dry ice
Effect of Ibr on microenvironment	Mandatory	Bone marrow aspirate	Green Top tube	5 mL (1)	Baseline/ after registration but prior to treatment	Prior to addition of len to ibr-dex* and as clinically indicated***	Confirmed disease progression	No	At room temperature
Effect of Ibr on microenvironment	Mandatory	Peripheral Blood	Green Top tube	5 mL (2)	Baseline/ after registration but prior to treatment	Every 3 cycles while patient continues on treatment**		No	At room temperature
Effect of Ibr on platelet aggregation (Platelet surface glycoprotein by flow cytometry, blood)	Mandatory	Peripheral Blood	Yellow Top tube	5 ml	Baseline/ after registration but prior to treatment	Every cycle for first 3 cycles; then every 3 cycles while patient continues on treatment for up to 12 cycles	Confirmed disease progression	Yes	At room temperature

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	Every cycle	End of treatment	Process at site?	Temperature Conditions for Storage /Shipping
Effect of Ibr on platelet aggregation Platelet aggregation study (functional)	Mandatory	Peripheral Blood	Special tubes to be supplied by heme lab	9 ml (4)	Baseline/ after registration but prior to treatment	Every 3 cycles while patient continues on treatment for up to 12 cycles	Confirmed disease progression	Yes	At room temperature

*Phase II only
**Additional samples to be drawn in-between every 3 cycles in case there is confirmed disease progression
*** Additional samples to be drawn if a bone marrow is done for confirmation of response or as otherwise clinically indicated.
ibr=ibrutinib, len=lenalidomide, dex=dexamethasone

14.2 Collection and Processing

No specific instructions other than outlined in table 14.1

14.3 Shipping and Handling

14.31 **Kits will not be used for this study.**

14.32 Shipping Specimens
Samples will be transported/shipped to Mayo Clinic in Florida at the following address:

Chanan-Khan laboratory
Attn: Aneel Paulus, M.D.
Griffin Building 164
4500 San Pablo Rd.
Jacksonville, FL 32224

14.33 Handling Specimens
Samples should be transported same day (if from Mayo Clinic, Florida) or shipped by overnight mail (if from Mayo Clinic in Arizona or Minnesota) on dry ice and dispatched only on Monday-Thursday for a receipt in Jacksonville on Tuesday-Friday.

14.4 Background and Methodology

14.41 BTK signalosome: The variability in the extent of clinical response may suggest underlying adaptability of the MM clone mediated through components of the BTK signalosome. Patients with B-cell malignancies treated with ibrutinib demonstrate upregulation of p-Akt and p-Erk (downstream mediators of BTK) in some (but not all) patients and suggest that these downstream pathways may contribute to the survival of the malignant clone.[18] They also concluded that these cells might not be dependent upon the proximal BTK pathways mediated apoptosis and thus resistant to killing by ibrutinib. To address this question we will establish the profile of BTK signalosome for each patient through determination of the mRNA (RT-PCR/ nanostring assay) and protein expression (western blot analysis) of members of the BTK signaling pathway. Samples: Bone marrow samples (2 x 5ml green top tubes) will be collected at prior to initiating the ibrutinib therapy, at the time of disease progression while on ibr therapy or if there is a lack of response noted to single-agent ibr at the time points specified in the study schema. In the form of expected results, we anticipate (a) variability in the expression and phosphorylation status of various members of BTK pathway (Syk, Lyn CD79 FYN) and their targets (ERK, AKT, NFKB and Bcl-2, Mcl-1, XIAP, MYC, CD40 and CFLAR) (b) and predict correlation of this variability with the depth of response achieved in that patient. Furthermore, this will also help identify the signalosome pattern that may suggest lack of response/progression to single-agent ibr in MM patients.

14.42 Effect of ibrutinib on MM microenvironment: In cancer redirection of host immunity from a predominant Th2 to Th1 response can deliver antitumor response. Ibr can bind to ITK, a member of the TEC-kinase family mediates TCR signaling through PLCg, NFAT, NF-kappaB and MAPK.[19] This results in activation and proliferation of CD8+ cells. Our hypothesis is that ibr alters the

Th2:Th1 balance in the blood and bone marrow microenvironment skewing towards a more Th1 profile and this may translate into its clinical efficacy. We further hypothesize that the robustness of the Th1 response will direct ibrutinib's depth of response. Blood and bone marrow will be evaluated/quantified for Th1 and Th2 cells (by flow cytometry). Changes in the cellular profile as well as respective cytokine (such as IL2, IL12, INFg and IL4, IL5, IL13 and IL10, respectively) will be measured (for cytokine we will use the multiplex assay). Blood (2 x 5ml green top tubes) and bone marrow samples (1 x 5ml green top tubes) will be collected at any time prior to initiating the ibrutinib therapy. Serial bone marrow samples will be collected at the time of disease progression while on ibr therapy or if there is a lack of response noted to single-agent ibr at the time points specified in the study schema. Furthermore, serial blood samples will be collected every 3 months while the patient remains on study treatment and additionally at the time of disease progression while on ibr therapy or if there is a lack of response noted to single-agent ibr at the time points specified in the study schema.

We anticipate that ibr treatment (a) will results in increase in Th1 cells both in the blood and the bone marrow with bone marrow demonstrating a higher percentage of Th1 cell activity and that (b) extent of immune cellular response will correlate with the robustness of the clinical response and that (c) the cytokine profile will mimic this cellular pattern and can be used to predict immune cellular response to ibrutinib. Identification / validation of immune restoration ability of ibr and its correlation with disease response will be a highly novel observation and will define a unique role and mechanism of ibrutinib in MM.

14.43 Effect of ibrutinib on platelet aggregation: While it is known that ibrutinib causes platelet dysfunction, the mechanistic pathway is not clearly understood. *In-vitro* studies have shown possible interaction with collagen receptor GPVI and also affect platelet adhesion on von Willebrand factor. To further characterize the bleeding events in ibrutinib-treated patients, we will investigate the effect of ibrutinib on platelet aggregation ex vivo. Platelet flow cytometric analysis is the preferred method to assess quantitative surface glycoprotein (GP) deficiencies. GP expression levels can be measured by using fluorescent-conjugated GP-specific antibodies and their fluorescent intensities can be compared to normal ranges of various glycoproteins. Platelet aggregometry uses a combination of laser light scattering to monitor the continuous formation of platelet microaggregates. The test is sensitive enough to detect aggregates containing only two or three platelets. The method uses of a panel of platelet agonists (eg, collagen, ADP, epinephrine, ristocetin) at a range of concentrations that triggers classical platelet responses, including shape change as well as primary and secondary aggregation. The recorded response depends upon the normal functioning of the platelet, the presence of inhibitors of platelet function, as well as the concentration of agonist, facilitating detection of classical platelet disorders based upon the pattern of aggregation.

15.0 Drug Information

15.1 Ibrutinib (Imbruvica™, PCI-32765)

15.11 **Background**: Ibrutinib is an antineoplastic agent that is an inhibitor of Bruton's tyrosine kinase.

15.12 **Formulation**: Ibrutinib comes in a different dosage forms.

- Capsules: either size 0, gray 140 mg capsules or size 2, yellow immediate-release 70 mg capsules. The capsules also contain the following compendial excipients: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. Capsules are packaged in high-density polyethylene bottles with an induction seal and a child resistant screw-top cap.

15.13 **Preparation and storage**:

- Ibrutinib capsules: 70 mg and 140 mg. store at 15°C to 25°C (59°F to 77°F) with excursions permitted to 30°C (86°F).

15.14 **Administration:** Administer orally with water at approximately the same time every day. Ibrutinib can be taken with or without food. Swallow capsules whole; do not open, break, or chew the capsules. Hazardous agent; use appropriate precautions for handling and disposal.

15.15 **Pharmacokinetic information**:
a) Absorption – Current data indicates bioavailability is low and displays high inter-subject variability. The median time to reach maximum plasma concentration (T_{max}) is approximately 2 hours. Administration of ibrutinib in a fasted condition resulted in approximately 60% of exposure as compared to administration either in fed condition (30 minutes after a high-fat breakfast), or when drug was taken 30 minutes before or 2 hours after a meal. Based on data for the effects of food, ibrutinib could be taken with or without food at approximately the same time each day. The effect of food on the PK of ibrutinib 560 mg tablets was similar to that observed for ibrutinib capsules.
b) Distribution: The plasma protein binding of ibrutinib and its metabolite PCI 45227 in human plasma is 97.3% and 91%, respectively. The apparent steady state volume of distribution is approximately 10,000 L.
c) Metabolism – Ibrutinib is extensively metabolized by CYP3A4/5 (major) and CYP2D6 (minor). Ibrutinib is metabolized in the liver.
d) Elimination –The excretion of ibrutinib is predominantly via the feces with approximately 80% recovered mostly within 2 days, whereas ~8% is excreted in urine. Approximately 1% of the ibrutinib is recovered as unchanged drug, all in feces. The half-life elimination is 4-6 hours. Overall, these PK characteristics resulted in minimal accumulation of both parent compound and metabolite PCI-45227 on repeated daily dosing of ibrutinib.
e) Special populations: a small increase in bioavailability was estimated with increasing age. Exposure is predicted to increase approximately 14% and decrease approximately 20% in subjects of 81 and 49 years of age, compared to a typical 67-year old subject. No statistically significant

effects were observed for the other covariates tested, i.e., sex, race, mild and moderate renal impairment, mild hepatic impairment and B-cell histology. The recommended doses for patients with mild and moderate liver impairment are 280 mg/day and 140 mg/day (Child-Pugh Class A and B, respectively). It is not recommended to administer ibrutinib to subjects with severe hepatic impairment (Child-Pugh Class C). Pediatric studies are still ongoing.

15.16 **Potential Drug Interactions**: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4/5. Voriconazole and posaconazole can be used concomitantly with ibrutinib as per the dosing guidance described in the specific clinical study protocol. All other strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, and cobicistat) should be avoided, and an alternative with less CYP3A inhibitory potential should be considered. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, see the recommended dose modifications described in the specific clinical study protocol.

If a moderate CYP3A inhibitor (eg, fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) is indicated in patients with B-cell malignancies, reduce the ibrutinib dose to 280 mg for the duration of the inhibitor use or as per recommended dose modifications described in the specific clinical study protocol. No ibrutinib dose modifications for moderate inhibitors are required in patients with cGVHD dosed with ibrutinib 420 mg.

No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A.

Administration of ibrutinib with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin and St. John’s Wort). Consider alternative agents with less CYP3A induction.

To minimize the potential for an interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

There have been reports of bleeding-related events in subjects treated with ibrutinib. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib unless specified in the protocol. Supplements such as fish oil and vitamin E preparations should be avoided.

Based on preliminary data from the combination studies of ibrutinib and venetoclax, venetoclax exposure (area under the concentration-time curve [AUC]) at 400 mg QD appears to be approximately 1.7 to 1.8-fold higher with 420 mg ibrutinib and approximately 3-fold higher with 560 mg compared with venetoclax single agent exposure. To date, no new safety signals have been identified in these ongoing combination therapy studies Patients should be closely monitored for signs of toxicity.

Evaluation of the effect of repeated administration of ibrutinib on the PK of oral contraceptives (OC), showed that the maximal daily dose of 560 mg did not lead to a decreased exposure of OC drugs ethinylestradiol(EE)/levonorgestrel in female subjects, suggesting that the OCs remain efficacious when used during ibrutinib therapy.

15.17 **Known potential toxicities**:

- **Very Common (≥10%):** neutropenia, thrombocytopenia, anemia, diarrhea, nausea, constipation, vomiting, decreased appetite, fatigue, peripheral edema, pyrexia, pneumonia, upper respiratory tract infection, arthralgia, back pain, headache, cough, dyspnea, rash
- **Common (1 to <10%):** febrile neutropenia, leukocytosis, lymphocytosis, atrial fibrillation, vision blurred, stomatitis, gastritis, asthenia, bronchitis, lung infection, sinusitis, urinary tract infection, neutrophil count decreased, platelet count decreased, dehydration, hyperuricemia, myalgia, extremity pain, dizziness, hematuria, epistaxis, erythematous rash, maculo-papular rash, hematoma, hypertension, cellulitis, infection, lower respiratory tract infection, sepsis, skin infection, arthritis, bone pain, flank pain, basil cell carcinoma, squamous cell carcinoma, syncope, acute kidney injury, pleural effusion, respiratory failure, macular rash, hypotension, respiratory tract infection, cardiac failure
- **Rare (<1%):** leukostasis syndrome, pancytopenia, atrial flutter, , myocardial infarction, colitis, intestinal obstruction, oral mucosal blistering, systemic inflammatory response syndrome, atypical pneumonia, bacteremia, infectious enterocolitis, neutropenic sepsis, periorbital cellulitis, pneumonia (pneumocystis jirovecii, bacterial, cryptococcal, fungal, haemophilus, influenzal, viral, pseudomonal klebsiella, legionella, parainfluenzae viral, streptococcal, organising), septic shock, urosepsis, post procedural hemorrhage, subdural hematoma, tumor lysis syndrome, pain (pelvic, groin), hemorrhage intracranial, lung infiltration, pneumonitis, pustular rash, breast cellulitis, bronchopulmonary aspergillosis, Escherichia sepsis, viral lower respiratory tract infection, pneumococcal sepsis, fungal sinusitis, staphylococcal infection, staphylococcal skin infection, interstitial lung disease, angioedema, hypertensive crisis , chronic sinusitis bacteroides bacteremia, orbital cellulitis, staphylococcal cellulitis, Escherichia bacteremia, alveolitis allergic, Stevens-Johnson syndrome, Haemophilus bacteremia/sepsis, pseudomonal lung infection, bacterial sepsis, herpes zoster disseminated, muscle hemorrhage, cerebral hemorrhage, deep vein thrombosis, squamous cell

carcinoma of the skin, basosquamous carcinoma of the skin, hepatic failure, ventricular tachyarrhythmia, basal cell carcinoma, neutrophilic dermatoses

- **Cardiac Arrhythmias:** Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment, and follow the dose modification guidelines
- **Cerebrovascular accidents:** Cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

Please refer to the prescribing information or Investigator's Brochure for a more complete comprehensive list of treatment-

15.18 **Drug procurement:** Drug will be provided free of charge to study participants by Pharmacyclics, Inc.

15.19a **Nursing Guidelines:**

- There are numerous drug to drug interactions. Record all of patient's medications including OTC, and herbal use. Avoid concomitant use with agents as listed in section 15.16.
- Patients should be instructed to avoid eating grapefruit (including juice) and Seville oranges while on ibrutinib.
- Peripheral edema is common. Instruct patients to report this to the study team.
- Gastrointestinal side effects are common (diarrhea, nausea, constipation, abdominal pain, vomiting, etc). Treat symptomatically and monitor for effectiveness of intervention.
- Monitor CBC w/diff. Instruct patients in energy conserving lifestyle (anemia) and to report any unusual bruising or bleeding and/or signs or symptoms of infection to study team.
- Arthralgias, Myalgias, and muscle spasm can be seen. Treat symptomatically and monitor for effectiveness.
- Monitor renal function/uric acid levels, especially in patients who may be experiencing dehydration.
- Respiratory symptoms may include, cough, SOB, and URI. Instruct patients to report these symptoms to the study team.
- Rarely patients can experience secondary skin cancers. Instruct patients to report any new skin lesions to the study team.

- Rash can be seen. Instruct patient to report to study team.
- Cardiac arrhythmias have been seen with this agent including a-fib, atrial flutter and ventricular tachyarrhythmia's, some of which have led to death. Instruct patients who experience any palpitations, lightheadedness, syncope, or SOB to see medical care immediately. This is especially important in patients who have pre-existing cardiac issues.
- Warn patients of the risk of bleeding. Patients should not take warfarin or other vitamin K antagonists while on ibrutinib, unless the protocol allows for it. Additionally, patients should be cautioned to avoid fish oil and vitamin E supplements.
- Patients who are concurrently on ibrutinib and ventoclax should be monitored closely for excess toxicity.
- Ibrutinib should be held at least 3-7 days pre and post-surgery, depending on type of surgery.
- There have been reports of CVA and TIA in patients on ibrutinib. Instruct patients to report any headaches and/or neurologic changes immediately or seek out emergency care.
- Patients may experience dry eyes, blurred vision or decreases in vision. Instruct patients to report this to the study team.

15.19b **Medications to be Used with Caution with Ibrutinib**

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.

- 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 10. 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.

QT Prolonging Agents

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

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 X.

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

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.

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.

Major Surgical Procedures

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

Emergency Procedures

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

15.2 Lenalidomide for Oral Administration (Revlimid®)

15.21 **Background**: Lenalidomide has antineoplastic, immunomodulatory and antiangiogenic characteristics via multiple mechanisms. Lenalidomide selectively inhibits secretion of proinflammatory cytokines (potent inhibitor of tumor necrosis factor-alpha secretion); enhances cell-mediated immunity by stimulating proliferation of anti-CD3 stimulated T cells (resulting in increased IL-2 and interferon gamma secretion); inhibits trophic signals to angiogenic factors in cells. Lenalidomide inhibits the growth of myeloma cells by inducing cell cycle arrest and cell death.

15.22 **Formulation and Dispensing**: Commercially available for oral administration as: Capsules: 5 mg, 10 mg, 15 mg and 25 mg

Lenalidomide is approved for marketing only under a FDA approved, restricted distribution program called Revlimid REMS. Physicians, pharmacies, and patients must be registered; a maximum 28-day supply may be dispensed; a new prescription is required each time it is filled; pregnancy testing is required for females of childbearing potential.

15.23 **Preparation, storage, and stability**: Store oral capsules at controlled room temperature between 15ºC and 30ºC (59 ºF and 86 ºF). Refer to labeling on the bottle for expiration date of the commercial tablets.

15.24 **Administration:** Refer to the treatment section for specific administration instructions. Administer with water. Swallow capsule whole; do not break, open, or chew.

15.25 **Pharmacokinetic information**:
Absorption: Rapid
Metabolism: Approximately two-thirds of Lenalidomide is eliminated unchanged through urinary excretion.
Protein binding: ~30%
Time to peak, plasma: Healthy volunteers: 0.6-1.5 hours; Myeloma patients: 0.5-4 hours
Half-life elimination: ~3 hours
Excretion: Urine (~67% as unchanged drug)

15.26 **Potential Drug Interactions**:
Increased Effect/Toxicity: Abatacept and Anakinra may increase the risk of serious infection when used in combination with Lenalidomide. Lenalidomide may increase the risk of infections associated with vaccines (live organism).
Decreased Effect: Lenalidomide may decrease the effect of vaccines (dead organisms).
Herb/Nutraceutical Interactions: Avoid echinacea (has immunostimulant properties; consider therapy modifications).

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Boxed Warnings:
1. Potential for human birth defects
2. Hematologic toxicity (neutropenia and thrombocytopenia)
3. Deep Venous Thrombosis and Pulmonary Embolism

Common known potential toxicities, >10%:
Cardiovascular: Peripheral edema
Central nervous system: Fatigue, pyrexia, dizziness, headache
Dermatologic: Pruritus, rash, dry skin
Endocrine & metabolic: Hyperglycemia, hypokalemia
Gastrointestinal: Diarrhea, constipation, nausea, weight loss, dyspepsia, anorexia, taste perversion, abdominal pain
Genitourinary: Urinary tract infection
Hematologic: Thrombocytopenia, neutropenia, anemia, myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction
Infection, especially when white blood cell count is low
Neuromuscular & skeletal: Muscle cramp, arthralgia, back pain, tremor, weakness, paresthesia, limb pain, muscle spasms
Ocular: Blurred vision
Respiratory: Nasopharyngitis, cough, dyspnea, pharyngitis, epistaxis, upper respiratory infection, pneumonia, shortness of breath

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Edema, deep vein thrombosis, hypertension, chest pain, palpitation, atrial fibrillation, syncope
Central nervous system: Insomnia, hypoesthesia, pain, depression
Dermatologic: Brusing, cellulitis, erythema
Endocrine & metabolic: Hypothyroidism, hypomagnesemia, hypocalcemia
Gastrointestinal: Vomiting, xerostomia, loose stools
Genitourinary: Dysuria
Hematologic: Leukopenia, febrile neutropenia, Lymphopenia
Hepatic: ALT increased
Neuromuscular & skeletal: Myalgia, rigors, neuropathy
Respiratory: Sinusitis, rhinitis, bronchitis, pulmonary embolism
Miscellaneous: Night sweats, diaphoresis

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Angioedema, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Tumor Lysis Syndrome, Graft vs. Host Disease, rhabdomyolysis, Kidney damage which may require dialysis

15.28 **Drug procurement:** As a requirement of the REMS program, access to Lenalidomide is restricted. Lenalidomide is approved for marketing only under a FDA approved, restricted distribution program called REVLIMID REMS (www.REVLIMIDREMS.com) formerly known as the RevAssist program. Physicians, pharmacies, and patients must be registered; a maximum 28-day supply may be dispensed; a new prescription is required each time it is filled; pregnancy testing is required for females of childbearing potential.

15.29 **Nursing Guidelines:**

- Myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction. Monitor CBC w/diff regularly. Instruct patient to report any unusual bruising or bleeding (thrombocytopenia); signs and symptoms of infection (neutropenia); and energy conserving lifestyle (anemia).
- Lenalidomide can have thrombotic adverse events (i.e DVT and PE). Instruct patient to report any limb swelling or pain, and to seek medical attention for shortness of breath or chest pain.
- Because of the potential for birth defects patients should be instructed in effective methods of birth control. Female patients should use 2 forms of birth control during treatment and for 4 weeks after discontinuing therapy. Males must be instructed to use a latex condom during any sexual contact with a woman of child bearing potential (even if they have had a vasectomy), because it is unknown if lenalidomide is present in semen.
- Patents may experience pruritus, rash and dry skin. Because of the rare risk of Steven's Johnson Syndrome, patients should immediately report any rash to their provider.
- Drug may cause hyperglycemia. Patients with diabetes or impaired fasting glucose may need to have their glucose levels monitored more closely.
- Gastrointestinal side effects (diarrhea, constipation, nausea, dyspepsia, anorexia, etc) are commonly seen. Manage patent symptomatically and monitor for effectiveness.
- Patients may experience myalgias, arthralgias, parasthesias, and other generalized pain. Administer analgesics as ordered and monitor for their effectiveness. Rarely infective bursitis and arthritis have been reported. Instruct patients to report any joint pain or redness to study immediately.
- Upper respiratory symptoms (nasopharyngitis, cough, epistaxis, etc.) can be seen. Manage symptomatically and monitor for effectiveness.
- Agent may cause fatigue, dizziness, vertigo or blurred vision. Instruct patient to report abdominal pain and/or jaundice to the study team.
- All prescribers and patients must be enrolled into the REVLIMID REMS program. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.
- Rarely secondary malignancies have been seen after lenalidomide therapy, including MDS, squamous/basal cell carcinomas of the skin, T-cell type acute leukemia.
- Monitor Renal function, renal failure has been reported.

15.3 Dexamethasone for Oral Administration (DXM)

15.31 **Background**: Dexamethasone is an adrenal corticosteroid compound. Dexamethasone decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

15.32 **Formulation**: Commercially available for oral administration as:
Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg
Solution, oral: 0.5 mg/mL (500 mL)
Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL)

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20ºC to 25ºC (60ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF. Store oral liquid at room temperature, do not freeze. Do not use if solution contains a precipitate. Refer to commercial package for drug expiration date.

15.34 **Administration:** Refer to the treatment section for specific administration instructions. May be taken with meals to decrease GI upset.

15.35 **Pharmacokinetic information**:
Onset of action: Prompt
Duration of metabolic effect: 72 hours
Metabolism: Hepatic
Half-life elimination: Normal renal function: 1.8-3.5 hours; **Biological half-life:** 36-54 hours
Time to peak, serum: Oral: 1-2 hours
Excretion: Urine and feces

15.36 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CYP3A4 (major); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (strong)
Increased Effect/Toxicity: Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.
Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.
Ethanol/Nutrition/Herb Interactions:
Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).
Food: Dexamethasone interferes with calcium absorption. Limit caffeine.
Herb/Nutraceutical: Avoid cat's claw, Echinacea (have immunostimulant properties)

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, frequency not defined:
Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances,

convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 **Nursing Guidelines:**

- Monitor regularly for hypertension, CHF and other evidence of fluid retention.
- Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.
- Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.
- Evaluate signs of infection, particularly local candidal infections and treat appropriately**.**
- Monitor blood glucose frequently.
- Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.
- Advise patient that easy bruising is a side effect.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a phase I/II study of a novel regimen of Ibrutinib, dexamethasone , and lenalidomide in patients with MM. The phase I portion is designed to determine the maximum tolerated dose (MTD) of ibrutinib that can be combined with lenalidomide and dexamethasone in patients with relapsed MM. The phase II portion is designed to assess the confirmed response rate of Ibrutinib, dexamethasone, and lenalidomide using a one stage phase II study design with an interim analysis in patients with transplant ineligible newly diagnosed MM.

Note: Phase II will not be initiated until after FDA review of Phase I data and approval to continue.

16.11 Primary Endpoint: The primary endpoint of the phase I portion of this trial is to assess the maximum tolerated dose (MTD). The primary endpoint of the phase II portion of this trial is the rate of confirmed response. A confirmed response is defined as a patient who has achieved an sCR, CR, VGPR, or PR on two consecutive evaluations at any time during treatment. Confirmed response will be evaluated using all cycles. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.12 Sample Size: This phase I portion of this study is expected to require a minimum of 6 and a maximum of 24 evaluable patients. For the phase II portion, the one stage study design with an interim analysis to be used is fully described below.

A minimum of 15 and a maximum of 34 evaluable patients will be accrued total onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 5 patients (2 phase I, 3 phase II) to account for ineligibility, cancellation, major treatment violation, or other reasons for a total of 63 patients overall.

16.13 Accrual Rate and Study Duration: The anticipated accrual rate is 2 evaluable multiple myeloma patients per month. At this rate, it will likely take about 3 months to enroll, treat, and evaluate each cohort of 3 patients in the dose escalation portion. We expect to evaluate a maximum of 4 dose levels, for a total duration of approximately 1.5 years in the dose escalation portion. The phase II patients are expected to accrue in the subsequent 1.5 years. The maximum total study duration is expected to be approximately 3.5 years, or until the last patient accrued has been observed for at least 6 months.

16.2 Phase I Portion Study Design:

This portion of the study will consist of a phase I trial to determine the MTD of ibrutinib in combination with lenalidomide and dexamethasone. A standard cohort of 3 phase I design will be utilized as described below. Three patients will be treated at each dose level and observed for a minimum of four weeks (i.e. one full cycle) before new patients are treated. Doses will not be escalated in any individual patient.

16.21 MTD Definition: MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% ($1-(1-0.25)^6$).

Refer to section 7.32 for determination of dose-limiting toxicity (DLT)

16.22 Dose Escalation: The dose escalation portion of this study will utilize a standard cohort of three design. The dose levels to which patients will be assigned in sequential cohorts are described in Section 7.3. The first cohort of three patients will be treated at dose level 1. Decisions on when and how to dose escalate are described below.

16.221 Three patients will be treated at a given dose level combination and observed for 1 cycle to assess toxicity.

16.222 If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.

16.223 If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded and further accrual will cease to

this cohort. If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

16.224 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

16.225 Dose de-escalation: If dose-limiting toxicity meets the stopping boundaries set by the above dose escalation algorithm at dose level 1 (for example, more than 1 out of 3 patients or more than 1 out of 6 patients), the next cohort of three patients will be entered at a dose level of -1. Further dose re-escalation will depend on the toxicity profile observed at these dose levels, and re-evaluation of the regimen by the study team may be done.

16.226 If a patient fails to complete the first cycle of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

16.227 Operating Characteristics for standard cohort of 3 design: The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the cohorts of 3 design described above.

True Rate of DLT (%)	Probability of Dose Escalation
10	0.91
20	0.71
30	0.49
40	0.31
50	0.17

16.23 Analysis Plans: All the relevant results pertaining to toxicity, MTD, response, timed endpoints and laboratory correlates will be examined in an exploratory and hypothesis-generating fashion. The small sample size and the heterogeneous patient population associated with phase I studies restricts the generalizability of the results. Any notable statistical result should only be viewed as preliminary evidence for further study in Phase II trials rather than a definitive finding in and of itself.

16.231 Adverse Event Profile

The number and severity of all adverse events (overall and by dose-level) will be tabulated and summarized in this patient population. The Grade 3+ adverse events will also be described and summarized in a similar

fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.

16.232 Toxicity Profile

The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading.

Overall toxicity incidence as well as toxicity profiles by dose level and patient will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

16.233 Response Profile

A response is defined to be a sCR, CR, VGPR, or PR noted as the objective status. Response will be evaluated using all cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

Responses will be summarized by simple descriptive summary statistics delineating depth of response as well as stable and progressive disease in this patient population

16.3 Phase II Statistical Design:

16.31 Decision Rule:

In a previous study of lenalidomide and dexamethasone in patients with transplant ineligible newly diagnosed multiple myeloma, 1076 patients were treated and evaluated for response.[29] The overall response rate in 541 patients treated with 18 cycles of lenalidomide and dexamethasone was 73%. In 535 patients who received continuous dosing of lenalidomide and dexamethasone until disease progression, the overall response rate was 75%. An increase in overall response rate for ibrutinib, dexamethasone, and lenalidomide would be of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 65%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 85%. The following one–stage design with an interim analysis is based on a two-stage Simon optimum design[30] and requires 34 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 65%

16.311 Interim Analysis: Enter 15 evaluable patients into the study. If 10 or fewer successes are observed in the first 15 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if the number of successes is at least 11, we will continue accrual.

16.312 Final Decision Rule: Enter an additional 19 evaluable patients into the study. If 25 or fewer successes are observed in the first 34 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 26, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies in this population.

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

16.314 NOTE: We will not suspend accrual at the interim analysis to allow the first 15 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.32 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .09, i.e. there is a 9% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping at the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.65	0.70	0.75	0.80	0.85
Then the probability of declaring that the regimen warrants further study is…	0.092	0.233	0.459	0.715	0.904
And the probability of stopping at the interim analysis is…	0.648	0.485	0.314	0.164	0.062

16.33 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.4 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.3) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 6 months.

16.41 Primary Outcome Analysis:

16.411 Definition: The primary endpoint of this trial is the confirmed response rate. A success is defined as a sCR, CR, VGPR, or PR noted as the objective status on two consecutive evaluations at any time. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.412 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.

16.413 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals

16.42 Secondary Outcome Analyses

16.421 Progression-free survival time is defined as the time from registration to the time of progression or death due to any cause. A progression that occurs during cycle 1 of the phase II portion prior to the addition of lenalidomide will not be considered an event. Patients who are alive and progression-free will be censored on the date of their last disease assessment. Patients who receive subsequent treatment for myeloma before disease progression will be censored on the date of their last disease assessment prior to initiation of the subsequent treatment. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.

16.422 Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier.

16.423 Duration of response is defined for all evaluable patients who have achieved a confirmed response as the date at which the patient's objective status is first noted to be a sCR, CR, VGPR, or PR to the earliest date progression is documented. The distribution of duration of response will be estimated using the method of Kaplan-Meier.

16.424 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.43 Exploratory Outcomes Analyses

16.431 Compliance to Treatment: Patient compliance to ibrutinib, dexamethasone, and lenalidomide will be assessed by means of self-reported and healthcare staff assessed pill count/diary. Correlation between medication adherence and disease response will be assessed.

16.432 Quality of Life (QoL): In the proposed trial, patient-reported QoL will be measured with the MD Anderson Symptom Inventory – Multiple Myeloma (MDASI-MM), which has been a validated tool.[24] The MDASI-MM consists of 13 core items, 7 MM-specific symptom severity items and 6 interference items; the time frame for addressing symptom severity and interference is the last 24 hours. From these items, mean subscale scores have been derived: mean Core (13 core items), mean Severity (13 core items + 7 MM-specific items), and mean Interference (6 interference items); an exploratory analysis in this study will examine a 4th score, the mean Severity score for the 7 MM symptoms. Response options range from 0 ("not present") to 10 ("as bad as you can imagine") for the severity items and from 0 ("did not interfere") to 10 ("interfered completely") for the interference items. These will be completed by patients in a paper or electronic entry at baseline (within 14 days of starting treatment), at the end of cycle 1 (± 3 days), at the end of cycle 6 (±3 days) and at completion of cycle 12 of treatment (±3 days), at any time the patient progresses while on the 3-drug regimen and is removed from the study protocol (within 14 days of removal from the study). The primary outcome of interest for this trial is the difference in the change of the mean Symptom Severity score for the Core plus 7 MM symptom items from baseline to the end of 6 cycles of therapy, and any variation reported in the MDASI-MM score at one year.

16.44 Exploratory Correlative Outcomes Analyses

16.441 BTK signalosome members (BTK, PLCy2, Lyn, Fyn, Syk, BLNK, BCAP, PI3K, NFkB, NFAT, pAKT and pS6) will be profiled by MSD-based mesoscale assay (or phospho-flow) at baseline before treatment, after cycle 1 (phase II patients only), and at the time of response assessment or disease progression. BTK signalosome component expression levels will be determined from BM and/or peripheral blood. Each measure will be summarized descriptively at each time point and changes across time will be evaluated. Correlation with response to overall therapy will be assessed using Wilcoxon's rank sum tests.

16.442 Ibrutinib has been shown to modulate T-cells populations (Th1, Th2 and T-Regs). Similarly, the combination of lenalidomide and dexamethasone is also known to act on these cell types. To understand the impact of this combination, we will conduct flow cytometry/FACS analysis to identify percentages of the immune cell populations (T-cells, NK cells, macrophages) in the bone marrow and peripheral blood at baseline before treatment, after cycle 1 (phase II patients only) and at the time of response assessment or disease progression. Each measure will be summarized descriptively at each time point and changes across time will be evaluated. Correlation with response to overall therapy will be assessed using Wilcoxon's rank sum tests.

16.5 Data and Safety Monitoring:

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data

for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules:

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Phase I: By the nature of the "cohorts of three" phase I study design, toxicity (i.e., adverse events that are possibly, probably or definitely related to study treatment) stopping rules are in place for each dose level. Specifically, if 2 or more dose-limiting toxicities (DLTs) are observed during Cycle 1 at any given dose level, accrual to that dose level will be stopped, and patients will be accrued to the next lower dose level until a maximum of 6 patients are treated at the lower level. Note that a DLT that affects dose escalation is only that which is observed in the first cycle of treatment. However, adverse events for all cycles will be reviewed and the study team will determine whether the dose level needs to be adjusted for future patients. Specifically, if one of the following occurs, then enrollment should stop and the trial should be re-evaluated whether to continue or close the trial permanently to accrual. The study team will evaluate all toxicities on all dose levels before determining how to proceed.

- if ≥1 in the first 3 patients experience a Grade 4 or higher non-hematologic adverse event at least possibly related to treatment over all cycles at any dose level
- ≥2 in the first 6 patients experience a Grade 4 or higher non-hematologic adverse event at least possibly related to treatment over all cycles at any dose level

Phase II: Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- if 5 or more patients in the first 15 treated patients experience a Grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 15 patients have been treated, 30% of all patients experience a Grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrials.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3.5 years after the study opens to accrual. The definition of "Primary Endpoint

Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.7 Inclusion of Women and Minorities:

16.71 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.72 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.73 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	21	41	62
Ethnic Category: Total of all subjects	**21**	**42**	**63**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	20	41	61
Racial Category: Total of all subjects	**21**	**42**	**63**

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Case Report Form packet.

18.2 Event monitoring

See Section 4.2 and data submission table in the case report form packet for the event monitoring schedule.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis prior to study entry as well as for evidence of response to study therapy and progression after study therapy. Supporting documentation for diagnosis will include either a pathology report or a laboratory report demonstrating multiple myeloma (including SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and Aspirate, skeletal bone survey, PET scan, Plasma Cell Proliferation and Assessment and FISH). These reports should be uploaded into the Supporting Documentation: Baseline form within 14 days of registration.

For progression of disease prior to study entry, supporting documentation includes the evidence needed to determine the patient's progression prior to enrollment. These documents should be uploaded into the Supporting Documentation: Baseline form within 14 days of registration.

For response to treatment, supporting documentation may include SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and aspirate, skeletal bone survey, and PET scan. These documents should be uploaded into the Supporting Documentation form.

For patients who progress after study therapy supporting documentation may include any of the following: SPEP, UPEP, FLC, serum and urine immunofixation, bone marrow biopsy and aspirate, skeletal bone survey, and PET scan. These documents should be uploaded into the Supporting Documentation form.

18.6 Labelling of materials

Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing

information is received. A list of the missing documents will be made available to the appropriate co-sponsor/participant.

18.8 Overdue lists

A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

19.0 Budget

19.1 Costs charged to patient: All routine clinical care. Ibrutinib will be provided free of charge by Pharmacyclics (an AbbVie company).

19.2 Tests to be research funded: Correlative studies outlined in Sections 14.0.

19.3 Other budget concerns: Protocol administration, study coordinator time, data management, and statistical analysis efforts will be funded by Pharmacyclics (an AbbVie company).

20.0 References

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Appendix I Myeloma Frailty Score

Variable	Patient Category	Score
Age	≤75 years	0
	76-80 years	1
	>80 years	2
Charlson Index (See Appendix III)	Charlson ≤1	0
	Charlson ≥2	1
Activities of Daily Living (ADL) Score (See Appendix II)	ADL >4	0
	ADL ≤4	1
Instrumental Activities of Daily Living (IADL) Score (see Appendix II)	IADL >5	0
	IADL ≤5	1

Additive Total Score	Patient Status
0	Fit
1	Intermediate fitness
≥2	Frail

Appendix II Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)

Score	ADL	IADL
0-1	Bathing (tub bath, shower, sponge bath)	Ability to use the telephone
0-1	Dressing (taking clothes from the wardrobe/drawers and getting dressed)	Shopping
0-1	Toileting (going to the toilet room, using toilet, arranging clothes)	Food preparation
0-1	Transferring	Housekeeping
0-1	Continence	Laundry
0-1	Feeding	Mode of transportation
0-1	-	Responsibility for own medications
0-1	-	Ability to handle finances

For each category, the patient receives a score of 1 if they can complete the activity and a score of 0 if they cannot complete the activity. The sum of each column is computed to get total scores for ADL and IADL.

Appendix III Charlson Comorbidity Index

http://www.uroweb.org/fileadmin/livesurgery/Charlson_Comorbidity_Index.pdf

AKA: Charlson Comorbidity Index, Comorbidity-Adjusted Life Expectancy

1. Indication
    1. Assess whether a patient will live long enough to benefit from a specific screening measure or medical intervention
2. Scoring: Comorbidity Component (Apply 1 point to each unless otherwise noted)
    1. Myocardial Infarction
    2. Congestive Heart Failure
    3. Peripheral Vascular Disease
    4. Cerebrovascular Disease
    5. Dementia
    6. COPD
    7. Connective Tissue Disease
    8. Peptic Ulcer Disease
    9. Diabetes Mellitus (1 point uncomplicated, 2 points if end-organ damage)
    10. Moderate to Severe Chronic Kidney Disease (2 points)
    11. Hemiplegia (2 points)
    12. Leukemia (2 points)
    13. Malignant Lymphoma (2 points)
    14. Solid Tumor (2 points, 6 points if metastatic)
    15. Liver Disease (1 point mild, 3 points if moderate to severe)
    16. AIDS (6 points)
3. Scoring: Age
    1. Age <40 years: 0 points
    2. Age 41-50 years: 1 points
    3. Age 51-60 years: 2 points
    4. Age 61-70 years: 3 points
    5. Age 71-80 years: 4 points
4. Interpretation
    1. Calculate Charlson Score or Index (i)
        1. Add Comorbidity score to age score
        2. Total denoted as 'i' below
    2. Calculate Charlson Probablity (10 year mortality)
        1. Calculate Y = e^(i * 0.9)
        2. Calculate Z = 0.983^Y
        3. where Z is the 10 year survival
5. References
    1. Charlson (1987) J Chron Dis 40: 373–83
    2. Gold (1994) J Clin Epidemiol 47: 1245–51

Appendix IV ECOG Performance Status Scale

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

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

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix V Creatinine Clearance (CrCl) Calculation

Cockcroft-Gault Equation:

$$\textbf{Creatinine clearance for males} = \frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$$

$$\textbf{Creatinine clearance for females} = \frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$$

Appendix VI New York Heart Association Classification of Congestive Heart Failure

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994. Original source: Criteria Committee, New York Heart Association , Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

Appendix VII Mayo Risk Stratification

High Risk

FISH deletion 17p

FISH t(14; 16)

FISH t(14; 20)

GEP (if done) High-risk signature

Intermediate Risk

FISH t(4:14)

Metaphase cytogenetic del 13

Hypodiploidy

Standard Risk

All others including:

FISH t(11; 14)

FISH t(6; 14)

Appendix VIIIa Patient Medication Diary (Phase I/Phase II)

(Phase I, all cycles and Phase II Cycle 2 and beyond)

PATIENT MEDICATION DIARY

Please complete this diary on a daily basis. Write in the amount of the dose of ibrutinib, lenalidomide and dexamethasone that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

If you experience any health/medical complaints or take any medication other than ibrutinib, lenalidomide or dexamethasone, please record this information.

Take the ibrutinib with water at about the same time every day (with or without food). Swallow the capsules whole; do not open, break, or chew the capsules. Please do not eat grapefruits or Seville oranges, or drink grapefruit juice while taking the ibrutinib.

Please take the dexamethasone with food.

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Ibrutinib							
Lenalidomide							
Dexamethasone							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Ibrutinib							
Lenalidomide							
Dexamethasone							

Week of: _____

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Ibrutinib							
Lenalidomide							
Dexamethasone							

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Ibrutinib							
Lenalidomide							
Dexamethasone							

Patient Signature: _____

My next scheduled visit is: _____

If you have any questions, please call: _____

HEALTH/MEDICAL COMPLAINTS

Please record all health/medical complaints you may have experienced below.

Please describe what you experienced	Date started	Date stopped

OTHER MEDICATION

Record only medication (prescription and/or over-the-counter, including herbal medications and vitamins) taken other than _____.

Name of Medication	Why did you take the medication?	Dose	Frequency

Study Coordinator Use Only

Verified by _____ Date_____

Appendix VIIIb Patient Medication Diary (Phase II, Cycle 1 Only)

PATIENT MEDICATION DIARY

Please complete this diary on a daily basis. Write in the amount of the dose of ibrutinib and dexamethasone that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

If you experience any health/medical complaints or take any medication other than ibrutinib or dexamethasone, please record this information.

Take your ibrutinib with water at about the same time every day (with or without food). Swallow the capsules whole; do not open, break, or chew the capsules. Please do not eat grapefruits or Seville oranges, or drink grapefruit juice while taking the ibrutinib.

Please take the dexamethasone with food.

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Ibrutinib							
Dexamethasone							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Ibrutinib							
Dexamethasone							

Week of: _____

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Ibrutinib							
Dexamethasone							

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Ibrutinib							
Dexamethasone							

Patient Signature: _____

My next scheduled visit is: _____

If you have any questions, please call: _____

HEALTH/MEDICAL COMPLAINTS

Please record all health/medical complaints you may have experienced below.

Please describe what you experienced	Date started	Date stopped

OTHER MEDICATION

Record only medication (prescription and/or over-the-counter, including herbal medications and vitamins) taken other than _____.

Name of Medication	Why did you take the medication?	Dose	Frequency

Study Coordinator Use Only

Verified by _____ Date_____

Appendix IX MDASI-MM Questionnaire

Date: _____ **Institution:**_____

Participant Initials: _____ **Hospital Chart #:**_____

Participant Number: _____

M. D. Anderson Symptom Inventory - Multiple Myeloma (MDASI - MM)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering** things at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Page 1 of 2

Date: _____ **Institution:**_____

Participant Initials: _____ **Hospital Chart #:**_____

Participant Number: _____

MM

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
14. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your **muscle weakness** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your **diarrhea (loose stools)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your **sore mouth or throat** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **rash** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your problem with **paying attention (concentrating)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your **bone aches** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***:

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
21. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
22. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
23. **Work** (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
24. **Relations** with other people?	○	○	○	○	○	○	○	○	○	○	○
25. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
26. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

Appendix X Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below.

Inhibitors of CYP3A	**Inducers of CYP3A**
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Bitter or Seville orange juice**	
verapamil	
voriconazole	
imatinib	
Weak inhibitors:	
cimetidine	
Fluvoxamine	

Inhibitors of CYP3A	Inducers of CYP3A
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

**Herbal weight loss supplements and/or dietary supplements containing bitter orange are also prohibited

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

Appendix XI Serum Calcium Corrected for Albumin

If calcium is expressed in mg/dL and albumin is expressed in g/dL:
Corrected calcium (mg/dL) = serum calcium (mg/dL) + 0.8 × (4 - serum albumin [g/dL])

If calcium is expressed in mmol/L and albumin is expressed in g/L:
Corrected calcium (mmol/L) = serum calcium (mmol/L) + 0.02 × (40 - serum albumin [g/L])

Source: Burtis 1999

Appendix XII 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 the oesophagus for bleeding oesophageal varices”. *The British journal of surgery*, 1973;60: 646-9.

Appendix XIII Patient Information Sheet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. You answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. The booklet contains one set of questions:
   MDASI-MM Questionnaire (26 questions)

2. Please select one answer for each question.

3. Please complete the booklet during your scheduled clinical visit and return it to your nurse or your physician

Thank you for taking the time to help us