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Carfilzomib, Lenalidomide, and Dexamethasone in High Risk Smoldering Multiple Myeloma: A Clinical and Correlative Pilot Study

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Drug Name:	Carfilzomib	Lenalidomide REVLIMID®	Dexamethasone
IND Number:	112587		
Sponsor:	Center for Cancer Research (CCR)		
Manufacturer:	Amgen, Inc.	Bristol Myers Squibb (BMS)	Generic
Supplier	Amgen, Inc.	BMS is providing commercial supply	CC Pharmacy

(BMS/Celgene tracking #: RV-MM-NCI-0719)

PRÉCIS

Background:

- SMM is a precursor condition to MM defined by the clinical parameters of M-protein ≥ 3.0 g/dL or bone marrow plasma cells ≥ 10% and absence of end organ disease.
- Risk of progression of high risk SMM at 5 years is 72-75% with median time to progression <2 years.
- The current standard of care for SMM is close follow-up without treatment until symptomatic MM develops. However, IMWG states "Preventive clinical trials need to be considered for patients with high risk smoldering myeloma".
- Carfilzomib is a new proteasome inhibitor with potent anti-MM effects

Objectives:

- To assess the response rate of CRd in patients with high-risk SMM, focusing on the MRD(-) CR rate

Eligibility:

- SMM according to the International Myeloma Working Group definition; i.e.:
  - Serum M-protein ≥3 g/dl and/or bone marrow plasma cells ≥10 % and <60%
  - Absence of anemia: Hemoglobin >10 g/dl
  - Absence of renal failure: serum creatinine < 2.0 mg/dL.
  - Absence of hypercalcemia: Ca <10.5 mg/dl or 2.65 mmol/L
  - Absence of lytic bone lesion
  - Involved/un-involved light chain ratio must be < 100
- Measurable disease as defined in the protocol
- "High-risk SMM" per Mayo Clinic, Spanish PETHEMA, or the Rajkumar, Landgren, Mateos criteria
- Age ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Adequate laboratory parameters as defined in the protocol

Design:

- Single arm pilot trial of combination therapy (carfilzomib, lenalidomide, and dexamethasone) for high risk smoldering multiple myeloma
- Patients will receive 8 cycles of induction combination therapy of CRd
- Each cycle consists of 28-days
- After 4 cycles of therapy, transplant eligible patients may choose to undergo stem cell collection
- After 8 cycles of CRd, patients will receive lenalidomide extended dosing (phase I) for 12 cycles. After 12 cycles, patients will have the option to continue extended dosing (phase II) for one additional year.

- Patients will have routine blood work with SPEP and free light chains monthly during the induction phase. Laboratory evaluations may be spread out to every 3 months during the maintenance and follow-up phases.
- Pre-treatment, post-treatment and follow-up bone marrow biopsies will be obtained for confirmation of diagnosis, response and correlative studies
- Patients will also undergo evaluation for minimal residual disease at regular interval time points, using multi-parametric flow cytometry and FDG PET-CT
- This single arm pilot study will plan on initially enrolling 12 evaluable patients to detect a VGPR from baseline. A replicate cohort of 16 evaluable patients will then be enrolled in order to more precisely define the response rate to the CRd regimen in this population. Accrual will then be extended to a total of 50 evaluable patients in order to estimate the MRD(-) CR rate with reasonable precision. To allow for a number of inevaluable patients and screen failures, the accrual ceiling will be set at 63.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To assess the response rate of CRd in patients with high-risk SMM, focusing on the minimal residual disease (MRD) negative complete response rate

1.1.2 Secondary Objectives

- To determine biochemical and symptomatic progression free survival (PFS)
- To determine duration of response (DOR)
- To determine duration of minimal residual disease (MRD) negative complete response (CR), and to estimate the rate of durable MRD(-) CRs (greater than one year)
- To evaluate toxicity of combination therapy (carfilzomib, lenalidomide, and dexamethasone)
- To evaluate biological activity of carfilzomib and correlate to clinical outcomes (gene expression profiling on pre- and post-carfilzomib exposure bone marrow samples) NOTE: This endpoint no longer applies as of Amendment H (version date 06/12/2017).
- To determine overall survival (OS)
- To compare the MRD (-) CR rates between patients enrolled from 2012-2014 vs. enrolled in 2017 and later years

1.1.3 Exploratory Objectives

- MRD detection by next generation VDJ sequencing, exome sequencing, and PD-1/PD-L1 expression in the bone marrow compartment

- To evaluate FISH data on available patients enrolled following amendment L (version date 05/17/2018) with respect to classification into high risk vs. non-high-risk patients
- To evaluate radiographic changes (FDG avidity) in bone marrow heterogeneity and focal infiltration by PET/CT at baseline and overtime
- To evaluate radiographic changes (signal intensity) in bone marrow heterogeneity and focal lesions by Diffusion Weighted MRI (DW-MRI) at baseline and over time

1.2 BACKGROUND AND RATIONALE

1.2.1 Introduction

Multiple myeloma (MM) is a neoplasm characterized by the proliferation and accumulation of malignant plasma cells in the bone marrow that lead to the overproduction of monoclonal proteins in the serum or urine, affecting nearly 20,000 people annually.[1] End-organ damage resulting from this disorder includes hypercalcemia, renal insufficiency, anemia, and lytic bone lesions.[5] Myeloma remains incurable, with a median survival of 3-4 years in the United States, although newer therapies appear to be improving survival.[2-4] Importantly, two recent studies have proven that all cases of MM are preceded by a premalignant state, monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM), although at this time the biological mechanism of this progression is not understood.[5, 6] Currently, clinicians do not have access to any established biological markers that reliably predict progression to myeloma in patients with MGUS. This study is designed to better understand these premalignant disorders and their progression to MM.

MGUS is a premalignant plasma cell proliferative disorder that is characterized by elevated monoclonal immunoglobulin (M-protein) < 3 g/dL and bone marrow plasma cells < 10% in the absence of any other plasma cell disorder.[7] Epidemiological studies have estimated the prevalence of MGUS as 3.2% in patients older than 50 years; these patients have a 1% annual risk of progression to MM.[8, 9] However, risk factors of M-protein ≥ 1.5 g/dL, non-IgG M-protein, and abnormal serum free-light chain ratio are known to confer a higher rate of progression (58% at 20 years).[10] Similar to MGUS, SMM is a precursor condition to MM defined by the clinical parameters of M-protein ≥ 3.0 g/dL or bone marrow plasma cells ≥ 10%. Its risk of progression is higher than that of MGUS, estimated to be an average of 10% annually.[11] SMM can be risk stratified into categories using Mayo Clinic risk criteria[12] and Spanish PETHEMA[13] risk criteria in addition to the high-risk criteria set forward by Rajkumar, Landgren, Mateos [14]. At 5 years, risk of progression to MM for high risk SMM patients, using the above risk models is 72-76%. Median time to progression for high risk SMM is less than 2 years[1].

The current standard of care for SMM is close follow-up without treatment until symptomatic MM develops. Using melphalan-prednisone in SMM, early treatment has not been found to delay progression to active disease or improve overall survival [15]. The first randomized phase III study using novel drugs (lenalidomide/dexamethasone vs. surveillance) in SMM was presented by the Spanish study group in December 2009 at the annual ASH meeting [16]. In May 2011, an intention to treat (ITT), interim analysis (n=58) presented at the International Myeloma Workshop in Paris [17] showed the following: 7% stringent complete remission (sCR), 7% CR, 10% very good partial remission (VGPR) and 57% partial remission (PR). After a median of 7 (range 1-21) cycles of lenalidomide maintenance, the sCR increased to 13%. In the treatment arm, 15 (25%) patients had progressive disease (median follow-up 22 months). In the surveillance arm, 28 (46%) patients progressed to active MM. Median time to progression (TTP) from inclusion was 25 months for the surveillance arm versus median not reached in the treatment arm ($p<0.05$).

1.2.2 Proteasomes and Bortezomib

In MM, proteasomes have been found to play a critical role in protein turnover and degradation, thereby affecting essential cell functions of cell cycle control, signal transduction, apoptosis, and stress responses. The 26S proteasome complex consists of the 20S barrel–like core and 19S regulating component. The 20S proteasome has three main catalytic domains that contribute to protein breakdown: chymotryptic-like activity site, tryptic-like activity site, and caspase-like activity site [18]. Inhibiting proteasomes in malignant cells lead to buildup of ubiquinated proteins, resulting in eventual cell death. Such inhibitor effects likely extend beyond just a simple over-accumulation of cell waste. Rather, proteasome inhibitors also exert direct effects on the myeloma microenvironment and enable neoplastic cells to "re-direct" cell proliferation/apoptotic signaling while overcoming drug resistance mechanisms.

Bortezomib is a dipeptide boronate reversible inhibitor of the chymotryptic domain of the 26S proteasome. In combination with other agents, bortezomib demonstrates a potent anti-myeloma effect in initial treatment of transplant and non-transplant candidates, as well as in relapsed/refractory disease settings [19, 20]. A recent phase I/II study shows promising efficacy of the novel combination: bortezomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma patients, with 74% of subjects achieving very good partial response (VGPR) or better [21].

Despite undisputable benefits of novel agents, bortezomib and others pose certain clinical challenges. Bortezomib drug toxicity is common with side effects including neuropathy, GI distress (diarrhea), myelosuppression (in particular thrombocytopenia) and herpes zoster re-activation. Bortezomib associated peripheral neuropathy can be experienced in up to 33% (Grade 1 and 2) and <18% (Grade 3 and 4) newly diagnosed multiple myeloma patients [22]. In the aforementioned phase I/II study, with combination bortezomib, lenalidomide, and dexamethasone, 80% of treated patients experienced sensory neuropathy all grades [21]. In addition, as increasing numbers of patients are treated with novel agents, drug resistance and refractoriness seems to present a significant dilemma. Myeloma patients refractory or resistant to bortezomib and at least one IMID (lenalidomide or thalidomide) demonstrate median overall survival and event free survival of 6 months and 1 month, respectively [23].

1.2.3 Investigational Drug Carfilzomib

Carfilzomib is a tetrapeptide ketoepoxide-based irreversible inhibitor that forms a covalent bond with N-terminal threonine residue of the chymotrypsin domain. Compared to bortezomib, carfilzomib demonstrates equal potency but greater selectivity for the chymotrypsin activity site over the tryptic and caspase domains. Also, carfilzomib is less reactive to non-proteasome proteases compared to bortezomib, likely contributing to lower levels of neuropathy and myelosuppression [24-26]. In vitro models suggest carfilzomib has activity against bortezomib resistant myeloma cell lines [25]. Carfilzomib can also work synergistically with dexamethasone to enhance tumor cell death [25]. A number of phase I and phase II studies are currently investigating carfilzomib toxicity and efficacy in multiple myeloma. One such phase Ib/II trial is examining combination therapy with carfilzomib, lenalidomide, and low dose dexamethasone in refractory/relapsed multiple myeloma patients. Based on this ongoing study, no MTD of carfilzomib was identified in the dose escalation portion of the study

their highest dose cohort received. Based on data from an interim analysis including 12 evaluable newly diagnosed MM patients (who received up to 8 cycles of carfilzomib, lenalidomide and dexamethasone), 83% achieved VGPR. Among 19 patients evaluable for toxicity, less than 1% patients experienced grade 1 peripheral neuropathy.

As of April 2020, carfilzomib has been examined in approximately 6,582 people in a research setting. It has been found that carfilzomib can cause a reactivation of hepatitis B virus. Additionally, there have been 4 cases of Progressive Multifocal Leukoencephalopathy (PML) possibly linked to Carfilzomib.

1.2.4 Proposed Study Investigation with Correlative Studies

Given carfilzomib's potent anti-myeloma activity and lack of peripheral neuropathy, we propose a pilot investigation study of combination therapy (Cycles 1-8 carfilzomib, lenalidomide and dexamethasone) in high-risk SMM patients followed by extended dosing with lenalidomide (for 12 cycles). Proposed correlative studies include gene expression profiling on CD 138 + pre- and post- carfilzomib plasma cells, identification of potential biomarkers (blood, urine, bone marrow aspirates), proteasome activity and ubiquination assays, and effects on downstream signaling targets.

Patients will also undergo evaluation for minimal residual disease at regular interval time points, using multi-parametric flow cytometry, FDG PET-CT, Diffusion weighted MRI (DW-MRI) and detection of clonality using heavy and/or light chain immunoglobulin rearrangement. Current response criteria in MM are often limited in predicting clinical response and duration of response, and minimal residual disease (MRD) use in MM is still under current investigation. Immunophenotyping of abnormal plasma cells using multi-parametric flow cytometry has prognostic value in the post-autologous stem cell transplantation setting, and patients achieving negative MRD flow status compared to those with residual positive MRD flow status had longer OS (median not reached vs. 89 months, $p = 0.002$). [22] Other techniques, such as, polymerase chain reaction (PCR) of Ig heavy chain (IGH) rearrangements and light chain genes have also been employed in evaluating for MRD and found to have prognostic significance in showing prolonged PFS after intensive therapy.[23] More recently, two important published meta-analysis data have suggested that MRD negative status ($\leq 10^{-5}$ sensitivity) is an important endpoint that is associated with improved direct clinical benefit, both in terms of PFS and OS [27, 28]. Furthermore, in the updated 2015 IMWG response criteria for multiple myeloma, both MRD negative CR and sustained MRD negative CR at 10^{-6} to 10^{-5} sensitivity are formal response categories signifying "deep" responses. There is limited published data on MRD status as surrogate marker in the smoldering myeloma setting.

FDG-PET CT has been valuable at localizing intramedullary and extramedullary disease in MM. FDG uptake is able to distinguish between active lesions and chronic disease, scar tissue, necrotic tissue, radiation changes, and other benign disease. The sensitivity of FDG-PET in detecting myelomatous involvement is approximately 85%, and its specificity is approximately 90%.[25] Along the lines of more advanced imaging techniques, DW-MRI has recently been found as a potential complementary imaging modality that focusses on the actual myeloma plasmacytoma disease rather than subsequent bone destruction. The MY-RADS group state that because skeletal survey and CT predominantly help to detect the destructive effects of myeloma on trabecular and cortical bone rather than disease within the bone marrow space, sensitivity and capability

as a restaging tool are inherently limited. [29] Myeloma infiltrates within bone marrow can be observed on CT if they lie within the marrow spaces adjacent to fatty bone marrow. However, in trabecular bone spaces (ie vertebral bodies), myeloma infiltrates are difficult to evaluate given factors including the trabeculae, degenerative changes, benign lesions, and osteoporosis. In contrast, MRI allows direct imaging of the bone marrow given its superb sensitivity, soft-tissue contrast, and early detection of focal myeloma lesions. Although PET/CT can also detect myeloma lesions, MRI is more sensitive especially with newer techniques, i.e. DW-MRI, which have shown a sensitivity of 77% compared to 47% for PET/CT. [30] Current whole-body MRI protocols can incorporate DW-MRI sequences that are sensitive to cellular density and viability and are important for disease detection and monitoring. Another benefit of DW-MRI sequences are that they are quick to perform (~30-45 minutes) and interpret. Finally, the relationship of apparent diffusion coefficient values with cell density has the potential to assess response to treatment and response heterogeneity prior to changes in lesion size. [31, 32] The recent MY-RADS recommendations were published in an attempt to promote standardization and decrease variations in the acquisition, interpretation, and reporting of whole-body MRI and allow better response assessments across cancer centers. MY-RADS recommendations do require validation within clinical trials, including assessments of reproducibility and therefore we will be guided by the group's recommendations especially in regard to MRI data acquisition and analysis protocols. [29]

Incorporating such techniques into prospective clinical trials may have a role in evaluating response to therapy.

Effective with Amendment G (version date 07/20/2015), bone marrow aspirate and biopsy will be obtained for research studies at the discretion of the PI.

1.2.5 Continuation of Lenalidomide

Since the initiation of the protocol new data has been published regarding the efficacy and safety of extended dosing with lenalidomide in multiple myeloma patients. Three double blind randomized control trials were published in the same May 2012 issue of NEJM showing that patients receiving extended dosing with lenalidomide (10-15 mg) after induction type regimens have a significant progression free survival benefit in the lenalidomide therapy arms[33-35]. Two studies (McCarthy et al. and Attal et al.) were conducted after autologous HSCT and one study (Palumbo et al.) assessed transplant ineligible patients after induction therapy with melphalan, lenalidomide and prednisone. Importantly, McCarthy and colleagues showed an overall survival benefit in patients receiving lenalidomide compared to placebo (15% vs. 23%, $p = 0.03$)[34]. A small increased risk of secondary primary malignancies (SPM) was noted in the lenalidomide groups compared to the placebo groups in all three trials with a cumulative incidence of SPMs 7-8% in the lenalidomide arms of the three studies [36]. However, it should be noted that such a risk has been well known and established in multiple myeloma patients receiving alkylator therapy, such as melphalan[37]. All three of the aforementioned randomized trials used lenalidomide after melphalan exposure, a significant and notable difference between our trial (12-C-0107) and theirs. Despite this increased risk of secondary malignancy, post ad hoc analysis for all three trials with second malignancies being scored as "events" still showed a significant event free survival benefit for

lenalidomide arms compared to placebo[33-35].

In a recent meta-analysis presented by Palumbo et al. at ASCO 2013[36] including over 3000 patients reporting SPM cumulative incidence from randomized phase III trials comparing Len vs. No Len treatments, the cumulative incidence rates of hematologic SPMs at 36 months was 1.4% Len vs. 0.4% No Len (HR 3.8, 95% CI 1.15-12.62, p = 0.029) and solid SPMs at 36 months was 2.6% Len vs. 2.9 % No Len (HR 1.1, 95% CI 0.62-2.00, p = 0.72). In a subset analysis, investigators reviewed specific treatment regimens. Cumulative incidence of hematologic SPMs at 36 months were consistently higher in regimens following lenalidomide + melphalan 1.8% vs. lenalidomide + cyclophosphamide 0.3% vs. lenalidomide alone 0.3% vs. melphalan alone 0.4% (HR 3.8, 2.11-6.86, p<0.001). Unfortunately, the meta-analysis did not account for duration of lenalidomide therapy. However, it does seem to imply there is an increased risk of SPM in patients exposed to both melphalan and lenalidomide agents. Our study does not have melphalan exposure. Therefore, extrapolating cumulative SPM incidence (7-8% in lenalidomide arm) from the published randomized lenalidomide maintenance trials[33-35] would likely be overestimating incidence in our population given the lack of melphalan exposure in our trial. Recently, colleagues from the Mayo Clinic published long-term results of their experience with lenalidomide and dexamethasone. They report a SPM incidence of 6.6% in a regimen that does not include melphalan. Furthermore, recent data show that the risk of SPM is inherently associated with plasma cell disorders independent of therapy. For example, MGUS patients have an increased risk of AML/MDS, which is the most common SPM reported in multiple myeloma patients[37].

Currently no direct study allows us to accurately estimate anticipated SPM incidence, however, based on prior studies, recent meta-analysis, and lack of melphalan exposure with lenalidomide, we would anticipate an incidence range of 5.2-8% with a median follow-up period of 3 years.

In accord with these recent publications, lack of alkylator exposure and a similar study design to the phase III Spanish PETHEMA Quiredex trial, we increased lenalidomide 10 mg extended dosing from the initially proposed 1 year to 2 years in patients that maintain their current clinical response and do not show signs of progression as outlined in Section **6.3** or reasons for removal from protocol therapy listed in Section **3.5**.

1.2.6 Patient Reported Outcome/Quality of Life: PROMIS

Patient-Reported Outcomes Measurement Information System (PROMIS) is a health-related patient reported outcome (PRO) quality of life measurement instrument that was developed by NIH/NCI to standardize patient-reported outcomes for national use by research clinicians. Two versions of PROMIS are available to researchers: computer-adaptive tests (CATs) and short forms.[38-43] The short forms are brief, static instruments that have demonstrated similar reliability to the longer, dynamic CATs, which provide precise measures for studying populations with widely varied responses and longitudinal self-report data. Each short form includes 4 to 8 items, measures reported health outcomes in the past 7 days on a Likert type scale and takes less than 5 minutes each to complete; collectively we anticipate the questionnaires chosen for this study to take approximately 20 minutes in total.

PROMIS instruments, measuring a broad range of health domains, have been validated for adults (≥18) with a variety of health conditions. Results of PRO for patients with RRMM treated with the carfilzomib, lenalidomide, dexamethasone regimen have been published before; however, will be explored additionally in this study.[44] The most important difference in the prior study was the patient population was relapsed/refractory. In the current study, we hope to gain insight into PROs in a relatively healthy population who otherwise would not be treated for smoldering myeloma outside of a clinical trial. Given that the standard of care for smoldering MM is observation, it is imperative to evaluate the effect of treatment on PROs.

NOTE: As of February 1, 2021 PROMIS surveys are no longer completed.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically or cytologically confirmed Smoldering Multiple Myeloma confirmed by the Principal Investigator in discussion with the Laboratory of Pathology, NCI or the Department of Laboratory Medicine, CC, as needed, and based on the International Myeloma Working Group Criteria[45]:

- Serum M-protein ≥3 g/dl and/or bone marrow plasma cells ≥10 % and <60%
- Absence of anemia: Hemoglobin >10 g/dl
- Absence of renal failure: serum creatinine < 2.0 mg/dL
- Absence of hypercalcemia: Ca <10.5 mg/dl
- Absence of lytic bone lesion on X-ray, CT, or PET/CT and not more than 1 lesion on spinal MRI (NOTE: At the discretion of the investigator, PET/CT may replace MRI in patients who have a contraindication to MRI.)
- Involved/un-involved light chain ratio must be < 100

2.1.1.2 Measurable disease within the past 4 weeks defined by any one of the following:

- Serum monoclonal protein ≥ 1.0 g/dl
- Urine monoclonal protein >200 mg/24 hour
- Serum immunoglobulin free light chain >10 mg/dL AND abnormal kappa/lambda ratio (reference 0.26-1.65)

NOTE: As of Amendment L (version date 05/17/2018), the primary endpoint is MRD(-) CR rate; therefore, per the discretion of the Principal Investigator, patients without measurable disease (e.g., M-spike <1) may also be enrolled. This is in line with the most recent IMWG MM response criteria.

2.1.1.3 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of carfilzomib in combination with lenalidomide in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

2.1.1.4 ECOG performance status ≤2 (Karnofsky ≥60%, see **APPENDIX A**)

2.1.1.5 Patients must have normal organ and marrow function as defined below:

- absolute neutrophil count (ANC) ≥1.0 K/uL

  NOTE: At the discretion of the investigator, patients with an ANC of 0.5 K/uL – <1.0 K/uL may also be enrolled if clinically appropriate (e.g., patients with a baseline neutropenia that is chronic and that does not cause complications).
- platelets ≥75 K/uL
- hemoglobin ≥ 8 g/dL (transfusions are permissible)
- total bilirubin ≤1.5 X institutional upper limit of normal
- AST(SGOT)/ALT(SGPT) ≤3.0 X institutional upper limit of normal (ULN)
- Serum creatinine ≤1.5 X institutional ULN. If serum creatinine is above 1.5 X ULN, Creatinine Clearance (CrCl) or eGFR (estimated glomerular filtration rate)

must be ≥ 50 ml/min.

- CrCl will be calculated by Cockcroft-Gault method. CrCl (calculated) = (140 – Age) x Mass (in kilograms) x [0.85 if Female] 72 x Serum Creatinine (in mg/dL).
- eGFR will be calculated by either of the following well established formulas: modification of diet in renal disease (MDRD) or the chronic kidney disease (CKD)-epidemiology collaboration (EPI) (institutional standard) equations.

- CrCl may also be determined by measuring a 24 hour urine collection The measured CrCl must be ≥ 50 ml/min.

2.1.1.6 In addition to having SMM, patients must also be classified as "high-risk SMM" per Mayo Clinic[12] or Spanish PETHEMA[13] criteria. NOTE: Criteria set forward by Rajkumar, Landgren, Mateos [14] may also be used to define high risk disease, namely clonal bone marrow plasma cells ≥10% and any one or more of the following:

- Serum M protein ≥30g/L
- IgA SMM
- Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes
- Serum involved/uninvolved FLC ratio ≥8 (but <100)
- Progressive increase in M protein level (evolving type of SMM; increase in serum M protein by ≥25% on 2 successive evaluations within a 6-month period)
- Clonal BMPCs 50%-60%
- Abnormal PC immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotypes
- t(4;14) or del(17p) or 1q gain
- Increased circulating PCs
- MRI with diffuse abnormalities or 1 focal lesion
- PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

2.1.1.7 All study participants must be registered into the mandatory REMS® program, and be willing and able to comply with the requirements of REMS®.

2.1.1.8 The effects of carfilzomib on the developing human fetus are unknown. The immunomodulatory agents used in this trial (i.e., lenalidomide) are known to be teratogenic. Women of child-bearing potential and men must agree to use adequate contraception. Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test within 10-14 days and again within 24 hours prior to

[†] A female of childbearing potential is a sexually mature female 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).

prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure; see **APPENDIX B**: Requirements for REMS. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. In regard to carfilzomib, FCBP and their male partners must agree to use at least one method of effective contraception for at least 30 days after the last dose of carfilzomib and males must agree to use contraception and not to donate sperm for at least 90 days after the last dose of carfilzomib.

2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents.

2.1.2.2 Concurrent systemic treatment or prior therapy within 4 weeks for SMM. **NOTE:** Treatment with corticosteroids for other indications is permitted

2.1.2.3 Patients with a diagnosis of MM as defined by the 2014 IMWG diagnostic criteria[45]

2.1.2.4 Contraindication to any concomitant medication, including antivirals, anticoagulation prophylaxis, tumor lysis prophylaxis, or hydration given prior to therapy

2.1.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to carfilzomib or lenalidomide agents used in study, such as bortezomib or thalidomide, in addition to patients with known allergy to sulfobutyl ether β-cyclodextrin (Captisol®).

2.1.2.6 Uncontrolled hypertension or diabetes

2.1.2.7 Pregnant or lactating females. Pregnant women are excluded from this study. The effects of carfilzomib on a developing human fetus are unknown. Lenalidomide is teratogenic with unknown potential for abortifacient effects. Breastfeeding women and women planning on breastfeeding may not participate. No studies of carfilzomib have been conducted on breast feeding women and it is not known if it is excreted in milk. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Carfilzomib/Lenalidomide, breastfeeding should be discontinued if the mother is treated with Carfilzomib/Lenalidomide.

2.1.2.8 Significant cardiovascular disease with NYHA Class II, III or IV symptoms, or hypertrophic cardiomegaly, or restrictive cardiomegaly, or myocardial infarction within 3 months prior to enrollment, or unstable angina, or unstable arrhythmia.

2.1.2.9 Active hepatitis B or C infection.

2.1.2.10 Has refractory GI disease with refractory nausea/vomiting, inflammatory bowel disease, or bowel resection that would prevent absorption.

2.1.2.11 Significant neuropathy >Grade 2 at the time of first dose or within 14 days of enrollment.

2.1.2.12 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations within 2 weeks that would limit compliance with study requirements.

2.1.2.13 History of other malignancy (apart from basal cell carcinoma of the skin, or in situ cervix carcinoma) except if the patient has been free of symptoms and without active therapy during at least 2 years or if, at the clinical discretion of the investigator, the risks of this study do not outweigh the potential benefits on a case to case basis.

2.1.2.14 Major surgery within 1 month prior to enrollment.

2.1.3 Recruitment Strategy

Participant sources will include NIH patient populations and outside physician referrals. Of note, our outside physician referral network has a high representation of minorities.

This protocol may also be abstracted into a plain language announcement and posted on NIH websites and on NIH social media platforms.

In addition, we will work with specialists from the NIH Clinical Center Office of Patient Recruitment to develop study-specific public service announcements (e.g., Twitter, Facebook, etc.) and informational fliers to be used for recruitment activities. All information to be posted or distributed publicly will be submitted to the IRB for review and approval in advance of use.

Investigators may also take part in online and in-person patient support groups and social media forums where patients gather for networking, general support and information about their disease. These groups and forums may also serve as indirect recruitment referral resources (e.g., investigators may provide information/links to publicly available resources for more information on clinical trials to which a patient may self-refer).

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

A waiver of consent for these activities has been requested in section **12.5.1**.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the patient has signed the screening consent for this study or the consent for study 01C0129 (provided the procedure is permitted on that study) on which screening activities may also be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

A complete history and physical examination with documentation of measurable disease and assessment of performance status using the ECOG scale must be performed prior to study entry.

The following studies and laboratory tests will be completed 4 weeks prior to study entry, unless otherwise noted:

- CBC with differential and reticulocyte count
- Acute Care (sodium, potassium, chloride, CO2, glucose, BUN, creatinine), Mineral (serum calcium, phosphate, magnesium and albumin) and Hepatic (alkaline phosphatase, ALT, AST, total and direct bilirubin) Panels, and CrCl calculation
- Uric acid, LDH, and Beta-2 Microglobulin
- Serum protein electrophoresis (SPEP) and immunofixation to assess for presence and quantity of monoclonal protein (M-protein)
- Random urine sample for protein electrophoresis (UPEP) and immunofixation to assess for monoclonal protein in the urine (Bence-Jones proteinuria). Collect a 24 hour urine sample if necessary for confirmation of Smoldering Multiple Myeloma diagnosis [i.e. if patient's serum monoclonal protein is not measurable (< 1.0 g/dl)].
- Serum free light-chain studies
- Quantitative immunoglobulins
- Viral serologies: Hepatitis B surface antigen and Anti Hepatitis C (HCV) antibody. If Anti HCV is positive, will follow with HCV RNA PCR
- If the patient does not meet Mayo Clinic criteria or the criteria set forth by Rajkumar, Landgren, Mateos for high-risk SMM, but he/she has evidence of immunoparesis, the patient will have to undergo a bone marrow core biopsy and/or aspirate with flow cytometry to determine high-risk disease as defined by the PETHEMA criteria. If a bone marrow aspirate is done at screening, then the sample can be processed for baseline assays (see **APPENDIX C**: Bone Marrow Aspirate Collection, Sorting and Storage) to minimize the number of bone marrow biopsies
- Serum or urine pregnancy test in women of child-bearing potential.
- 12-lead EKG
- A skeletal survey of the axial and appendicular skeleton will be performed. (**NOTE:** A skeletal survey does not have to be repeated if performed at the NIH within 3 months of screening.)
- A spinal MRI (cervical/thoracic/lumbar) is required prior to study entry to exclude ≥ 2 lytic lesions; if patient has had an MRI performed at an outside facility, one performed at

NIH is not required but may be performed for research purposes. (NOTE: At the discretion of the Principal Investigator, PET/CT may replace MRI in patients who have a contraindication to MRI.) (**NOTE:** An MRI does not have to be repeated if performed at the NIH within 3 months of screening.)

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) will not be rescreened.

2.4 TREATMENT ASSIGNMENT AND RANDOMIZATION/STRATIFICATION PROCEDURES

2.4.1 Cohorts

Number	Name	Description
1	Multiple myeloma	Smoldering multiple myeloma patients with high-risk disease

2.4.2 Arms

Designation	Name	Description
A	Experimental: Treatment (Carfilzomib, Revlimid and Dexamethasone)	Carfilzomib (IV, Days 1, 2, 8, 9, 15, and 16 of the 28-day cycle); Revlimid (PO, Days 1-21 of the 28-day cycle; exception: not given on cycle 1 day 1); and, Dexamethasone (PO or IV, Days 1, 2, 8, 9, 15, 16, 22, and 23 of the 28-day cycle; exception: not given on cycle 1 day 1) (NOTE: Closed upon activation of Amendment H version date 06/12/2017.)
B	Experimental: Treatment (Carfilzomib, Revlimid and Dexamethasone)	Carfilzomib (IV, Days 1, 2, 8, 9, 15, and 16 of the 28-day cycle); Revlimid (PO, Days 1-21 of the 28-day cycle); and, Dexamethasone (PO or IV, Days 1, 2, 8, 9, 15, 16, 22, and 23 of the 28-day cycle) (NOTE: Opened effective with Amendment H. version date 06/12/2017)

2.4.3 Treatment Assignment and Randomization/Stratification

Single arm/group assignment; open-label and non-randomized.

2.5 BASELINE EVALUATION

Research and clinical laboratory tests to be performed prior to starting therapy. Refer to Section **5** for details on biospecimen collection and correlative studies.

2.5.1 Echocardiogram, Pro Brain-type natriuretic peptide (BNP) PT, PTT, and Troponin

2.5.2 Bone Marrow

- Histopathological evaluation on bone marrow aspirate and biopsy
- Immunophenotyping of aberrant clonal plasma cells by multiparametric flow cytometry.
- Interphase FISH/cytogenetics (If previously done, repeat not necessary)
- CD 138+ fractions and CD 138- fractions cell sorting with subsequent correlatives on both fractions to be done in the Young Lab.
- Proteasome activity and quantification (peripheral blood and bone marrow).
- Immunoglobulin heavy and/or light chain rearrangement.

2.5.3 Peripheral Blood, Urine, and Imaging

- Peripheral blood and urine samples for storage and establishing a biobank. (See **APPENDIX D**APPENDIX D: Peripheral Blood and Urine Collection and Storage)
- Subunit profiling and activity of circulating proteasomes by enzyme-like immunosorbent assay (optional).
- Apoptosis assays to identify necrotic or late stage apoptotic cells.
- Immunolocalization studies.
- Peripheral blood flow cytometry assessing for circulating plasma cells under the direction of Hao-Wei Wang, MD
- Peripheral blood will be assessed for immune cell populations including, but not limited to T cells (CD4 and CD8), LGL, and NK cells using flow cytometry.
- FDG PET/CT scan within 4 weeks of study entry and prior to starting therapy. NOTE: See additional information in Section **5.1.3**
- Diffusion Weighted Whole Body (DW-MRI) (exception: patients with a contra-indication or inability to perform due to administrative or logistical reasons

2.5.4 Questionnaires/Patient-Reported Outcomes (PROs)

NOTE: See Section **5**

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

Patients with high risk SMM will be enrolled on the pilot study and treated with 3-drug combination (Cycles 1-8 carfilzomib 20/36 mg/m^2, lenalidomide 25 mg, dexamethasone 20 mg cycles 1-4 and 10 mg cycles 5-8) followed by extended lenalidomide dosing.

All ongoing testing and procedures will take place per the Study Calendar, Section **3.4**. **NOTE:** Treatment is planned to be administered on an outpatient basis. At the investigator's discretion (e.g., for additional monitoring, patient social reasons, etc.), patients may be treated on an

inpatient basis. Any cases of planned hospitalization are not considered reportable serious adverse events per Section **8.4**.

3.1.1 Cycles 1-4 and 5-8

- Cycle 1 ONLY: Carfilzomib 20 mg/m^2 per dose, days 1 and 2; Carfilzomib 36 mg/m^2 per dose, days 8, 9, 15, and 16
- Cycles 2-8: Carfilzomib 36 mg/m^2 per dose, days 1, 2, 8, 9, 15, and 16
- Cycles 1-8: Lenalidomide 25 mg/day, days 1–21 every 28 days
- Cycles 1-4: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15, 16, 22, and 23
- For patients who choose to undergo stem cell harvest, the next cycle may be delayed for up to 5 weeks.
- Cycles 5-8: Dexamethasone 10 mg/dose, days 1, 2, 8, 9, 15, 16, 22 and 23 followed by extended lenalidomide

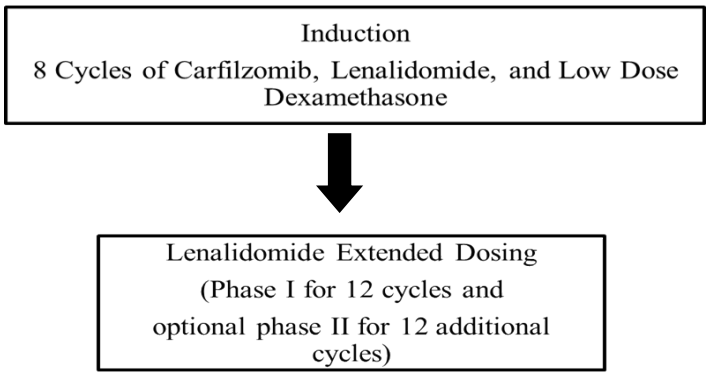
After receiving first 4 cycles, patients who are considered to be eligible for subsequent high dose therapy/autologous stem cell transplant (ASCT) will be encouraged to undergo autologous stem cell harvesting for potential use in the future. In accord with current clinical standards, the decision whether a given patient is eligible for subsequent high dose therapy/ASCT, or not, will be based on a clinical assessment conducted by the transplant center that evaluates the patient.

3.1.2 Maintenance and Ongoing Treatment or Follow-Up

After 8 cycles, patients will proceed to extended dosing phase I of lenalidomide (Days 1-21 of 28 day cycle) for 12 cycles. After 12 cycles of extended dosing of lenalidomide, patients who maintain their current clinical response and do not meet criteria of PD as defined in Section **6.3** will have the option to continue lenalidomide as clinically indicated for an additional year on extended dosing phase II.

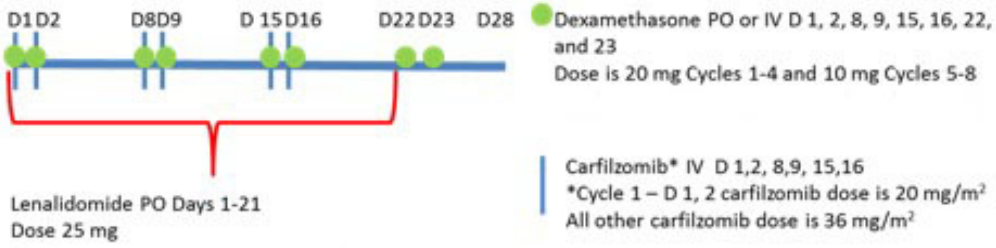
After 2 years of maintenance, patients will be followed by clinical and laboratory examination every 3-6 months until disease progression requiring treatment. If patients progress, they may be contacted by phone or email to gather survival information. (Note: patients who have not progressed after 2 years of maintenance therapy, but decide to continue lenalidomide maintenance at an outside facility, may also be followed on this protocol as above for long term follow-up at the discretion of the investigator. This follow up will consist of clinic and laboratory examination, however, if the patient is undergoing these investigations at an outside facility, follow-up can be limited to NIH investigator-patient or NIH investigator-outside physician communication of test results.)

Of note: On October 19, 2015, the study was closed to accrual for administrative reasons. Eighteen patients had enrolled at that time. Effective with Amendment H (version date 06/12/17), the study status will change to “Open-Recruiting” to allow for enrollment of the remaining 10-12 patients as per the statistical analysis plan of this protocol.



3.2 DRUG ADMINISTRATION

3.2.1 Induction Phase: Cycles 1-8 with 28 day cycles



3.2.2 Agents

3.2.2.1 Carfilzomib

- Cycle 1: 20 mg/m^2 IV infusion over 30 minutes on days 1 and 2, then 36 mg/m^2 IV on days 8, 9, 15, and 16
- Cycle 2-8: 36 mg/ m^2 IV infusion over 30 minutes on days 1, 2, 8, 9, 15, and 16
- See Section **14.1.3** for drug formulation and preparation instructions

3.2.2.2 Lenalidomide

- Cycle 1-8: 25 mg oral days 1-21 of 28-day cycle
- Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.
- If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.
- Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.
- Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers (unless they continue lenalidomide maintenance at an outside facility). Lenalidomide will be provided in accordance with the REMS® program of Celgene/BMS Corporation. Per standard REMS® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this

trial, must be registered in and must comply with all requirements of the REMS® program. Prescriptions must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each **cycle.**

3.2.2.3 Dexamethasone

- Cycles 1-4: 20 mg oral or IV on days 1, 2, 8, 9, 15, 16, 22, and 23
- Cycles 5-8: 10 mg oral or IV on days 1, 2, 8, 9, 15, 16, 22, and 23

In Cycle 1, the following supportive care measures will be implemented:

- Hydration will be administered prior and subsequent to carfilzomib dosing.
    - Oral hydration: All subjects must be well hydrated (i.e., volume replete). Begin oral hydration equal to approximately 30 mL/kg/day (~6–8 cups of liquid per day), starting 48 hours prior to the planned first dose of carfilzomib.
    - IV hydration: 500 mL (250 mL before & 250 mL after carfilzomib) OR 1000 mL (500 mL before & after carfilzomib) of normal saline or other appropriate IV fluid formulation must be given before *and* after each carfilzomib dose during Cycle 1. Total volume will be determined at the discretion of clinician and volume status of patient.
- In subjects considered to be still at risk for TLS at completion of Cycle 1, hydration should be continued into subsequent cycles if clinically indicated.

3.2.3 Harvesting Stem Cells

- After receiving first 4 cycles, patients who are considered to be eligible for subsequent high dose therapy/autologous stem cell transplant (ASCT) will be given the option to undergo autologous stem cell harvesting (not as part of this protocol) for potential use in the future.
- Collection and delivery can be conducted at outside institutions. In accord with current clinical standards, the decision whether a given patient is eligible for subsequent high dose therapy/ASCT, or not, will be based on a clinical assessment conducted by the transplant center that evaluates the patient.
- If harvesting and delivery of high dose therapy/autologous stem cell transplant is conducted at NIH Clinical Center, it will be conducted under a separate protocol.
- Transplant eligible patients will be defined as age <75 years with no significant disease co-morbidities and ECOG ≤2.
- For patients who choose to undergo stem cell harvest, next cycle may be delayed for up to 5 weeks.

3.2.4 Extended Dosing Phase I: Cycles 9-20

- Patients will go on to receive extended dosing with oral lenalidomide 10 mg/dose, given daily for 21 days of a 28 day cycle, for 12 cycles.
- Lenalidomide ordered in the extended dosing phase of the study will be prescribed by NIH Clinical Center physicians in one month increments for all patients. Upon completion of phone counseling per the REMS® program, the NIH Clinical Center

physician will prescribe a 28 day supply of lenalidomide to be sent to the patient by express delivery.

- For FCBP patients in the extended dosing phase of the study, lenalidomide will be prescribed by NIH Clinical Center physicians in one month increments. FCBP patients will still be required to have medically supervised pregnancy testing as outlined in **APPENDIX B**APPENDIX B: Requirements for REMS; and may have the pregnancy test performed by local treating physician. In these cases, the local physician will submit the results to NIH Clinical Center for review. Upon receipt of negative pregnancy test result and completion of phone counseling per the REMS® program, NIH Clinical physician will prescribe a 28-day supply of lenalidomide to be sent to the patient by express delivery.

3.2.5 Extended Dosing Phase II (optional): Cycles 21through 32 (effective with Amendment C version date 07/11/2013):

- After 12 cycles of extended dosing of lenalidomids (phase I), patients who maintain their current clinical response and do not meet criteria of PD as defined in Section **6.2** will have the option to continue lenalidomide 10 mg/dose as clinically indicated for one additional year. For those patients who are ready to begin extended dosing phase II, treatment may be delayed until amendment C (version date 07/11/2013) is approved by the IRB.
- Lenalidomide will be ordered in extended dosing phase II will be prescribed by NIH Clinical Center physicians in one month increments for all patients. Upon completion of phone counseling per the REMS® program, the NIH Clinical Center physician will prescribe a 28 day supply of lenalidomide to be sent to the patient by express delivery.
- For FCBP patients in the extended dosing phase of the study, lenalidomide will be prescribed by NIH Clinical Center physicians in one month increments. FCBP patients will still be required to have medically supervised pregnancy testing as outlined in **APPENDIX B**; and may have the pregnancy test performed by local treating physician. In these cases, the local physician will submit the results to NIH Clinical Center for review. Upon receipt of negative pregnancy test result and completion of phone counseling per the REMS® program, NIH Clinical physician will prescribe a 28 day supply of lenalidomide to be sent to the patient by express delivery.
- The duration for extended dosing was determined based on the study design from the Phase III trial Quiredex trial of lenalidomide/dexamethasone followed by lenalidomide maintenance vs. observation in high-risk SMM patients conducted by the Spanish PETHEMA study group. In this study, the treatment arm received 9 cycles of induction therapy with lenalidomide and dexamethasone followed by lenalidomide maintenance. In August of 2011, the Quiredex protocol was amended to stop lenalidomide maintenance treatment after 2 years. In addition, the three largest randomized phase III trials investigating lenalidomide maintenance were published in 2012 with median follow-up periods ranging from 30 months to 45 months. Two out of three of these studies continue lenalidomide maintenance until progression with no planned end date for lenalidomide maintenance[29,30].

3.3 DOSE MODIFICATIONS

NOTE: If patients require lenalidomide dose reductions and experience delays in drug administration (e.g., due to pharmacy not having the correct dosage form and/or time required to get the correct/adjusted dose supply to the patient), these administrative delays will not be considered a reportable protocol deviation. Furthermore, appointments and treatments missed by patients due to logistical reasons including weather and transportation problems will not be considered a reportable protocol deviation. Patients may miss up to 15% of lenalidomide doses. All efforts will be made to attaining and delivering medications to the patient expeditiously.

3.3.1 Dose Reductions: Induction Phase

	Lenalidomide	**Carfilzomib**	**Dexamethasone**	
			Cycles 1-4	**Cycles 5-8**
Baseline dose	25 mg daily on Days 1-21 of 28 day cycle	36 mg/m^2	20 mg	10 mg
One level dose reduction	20 mg daily on Days 1-21 of 28 day cycle	27 mg/m^2	10 mg	4 mg
Two level dose reduction	15 mg daily on Days 1-21 of 28 day cycle	20 mg/m^2	4 mg	0 mg
Three level dose reduction	10 mg daily on Days 1-21 of 28 day cycle		0 mg	
Four level dose reduction	5 mg daily on Days 1-21 of 28 day cycle			

3.3.1.1 Lenalidomide and Carfilzomib dosages are not modified in concert; i.e., lenalidomide and carfilzomib dosage reductions are implemented separately. If more than 2 dose reductions are required with Carfilzomib, study treatment will be discontinued and the patient will go off therapy.

3.3.1.2 If there is no resolution of toxicity after 2 weeks of withholding treatment or up to 3 weeks for infection related treatment, the subject will go off therapy

3.3.2 Hematologic Toxicity: Induction Phase

3.3.2.1 Due to the nature of the disease originating in the bone marrow, events occurring within the first two cycles of treatment and deemed to be due to disease burden will be exempt from dose reductions at the discretion of the investigator.

3.3.2.2 On day 1 of each new cycle (or day 1 of every third cycle during extension phase), patients must meet the following criteria or dose modify based on dose reductions in table 3.3.1:

- ANC $\geq 1.0 \times 10^9$ /L
- Platelet count $\geq 75 \times 10^9$ /L during cycles 1-8; Platelet count $>50 \times 10^9$/L during cycles 9 and beyond

If these conditions are not met on Day 1 of a new cycle, a new cycle of treatment will not be initiated until the toxicity has resolved. If there is no resolution after 2 weeks of withholding treatment or up to 3 weeks for infection related treatment, the subject will go off therapy.

If the investigator chooses to dose reduce according to table 3.3.1, the investigator will determine which drug will be modified based on side effect profile and clinical judgment.

3.3.2.3 If a patient develops thrombocytopenia or neutropenia during the cycle, then the following actions would take place (see Thrombocytopenia/Neutropenia table below).

Thrombocytopenia	**Lenalidomide**	**Carfilzomib**
Fall to < 25 x 10^9/L	Hold both Lenalidomide and Carfilzomib, follow CBC weekly. Hold prophylactic anti-coagulation.	
Return to ≥ 25 x 10^9/L	Resume lenalidomide at next dose reduction	Resume carfilzomib at full dose*
Subsequent fall to < 25 x 10^9/L	Hold both Lenalidomide and Carfilzomib, follow CBC weekly. Hold prophylactic anti-coagulation.	
Return to ≥ 25 x 10^9/L	Resume lenalidomide at next dose level reduction	Resume carfilzomib at full dose*

*Carfilzomib may be dose reduced at the clinical discretion of investigator

Neutropenia (Absolute Neutrophil Count)	**Lenalidomide**	**Carfilzomib**
Falls to < 0.5 x 10^9/L or to < 1.0 x 10^9/L with fever	Hold Lenalidomide and Carfilzomib. Add filgrastim if Grade 3 with fever (single temperature of 38.3ºC or sustained temperature of 38ºC for > 1 hour) or Grade 4. Follow CBC weekly	
Returns to ≥ 1.0 x 10^9/L	Resume Lenalidomide at next dose reduction.	Resume Carfilzomib at full dose*
Subsequent drop to < 0.5 x 10^9/L or to < 1.0 x 10^9/L with fever	Hold Lenalidomide and Carfilzomib. Add filgrastim if Grade 3 with fever or Grade 4. Follow CBC weekly	
Returns to ≥ 1.0 x 10^9/L	Resume Lenalidomide at next dose reduction.	Resume Carfilzomib at full dose*

*Carfilzomib may be dose reduced at the clinical discretion of investigator.

3.3.3 Non-Hematologic Toxicity: Induction Phase

3.3.3.1 Toxicity ≥ grade 3 will require appropriate study drug to be held until resolved to ≤ Grade 1 unless specified below. Investigator will determine which drug will be held based on side effect profile and clinical judgment.

3.3.3.2 Once toxicity has resolved ≤ grade 1, subsequent doses will be reduced at next dose level (according to table in section 3.3.1) if the adverse event was deemed to be treatment related by the PI. If the adverse event was deemed to be unrelated to treatment, the patient may continue the full dose.

3.3.3.3 Readily reversible electrolyte and metabolic abnormalities, infections or diarrhea controlled by appropriate therapy are exempt.

3.3.3.4 Patients with Grade 3 or higher peripheral neuropathy, Grade 3 or higher non-blistering rash or blistering rash of any grade, grade 3 or higher hypersensitivity reactions will be removed from protocol therapy.

Lenalidomide Toxicities	**Dosing Modifications**
Blistering Rash (Any Grade)	Discontinue lenalidomide and remove patient from therapy
Venous thrombosis/ embolism	Hold lenalidomide and start therapeutic anticoagulation. Restart lenalidomide at investigator's discretion at current dose level.
Renal Dysfunction CrCl based on Cockcroft-Gault. (Alternatively, MDRD or CKD-epi formulas may be used to estimate eGFR as more accurate indictors of renal dysfunction than CrCl in discrepant cases)	• CrCl 31-50 ml/min – Dose reduce lenalidomide to 10 mg daily from Days 1-21 • CrCl ≤30 mL/min (not requiring dialysis) – Dose reduce Lenalidomide to 15 mg every 48 hours • CrCl ≤30 mL/min (requiring dialysis) – Decrease Lenalidomide to 5 mg daily and on dialysis days give lenalidomide dose after dialysis.

Carfilzomib Toxicities	**Dosing Modifications**
Allergic Reaction/Hypersensitivity	Grade 2: Hold carfilzomib until ≤ Grade 1 and resume at full carfilzomib dose
Tumor Lysis Syndrome (≥ 3 of the following: ≥50% increase in creatinine, uric acid, or phosphate; ≥30% increase in potassium; ≥20% decrease in calcium; or 2-fold increase in LDH	Hold carfilzomib until all abnormalities in serum chemistries have resolved. Resume at full dose
Herpes zoster or simplex of any grade	Hold carfilzomib until lesions are dry. Resume at full dose
Neuropathy	Grade 2 treatment emergent neuropathy with pain: Hold carfilzomib until resolved to ≤ Gr 1 without pain. Then restart at next dose level reduction.
Congestive Heart Failure	Any subject with symptoms of congestive heart failure, whether or not drug related, must have the dose held until resolution or return to baseline. After which, treatment may continue at reduced dose or patient may be withdrawn from therapy.
Renal Toxicity: Serum creatinine ≥ 2 × baseline, or Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for hemodialysis	Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance). *If attributable to carfilzomib,* resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction. *If not attributable to carfilzomib,* dosing may be resumed at the discretion of the physician. For patients on hemodialysis receiving carfilzomib, the dose is to be administered after the hemodialysis procedure.
If Posterior Reversible Encephalopathy Syndrome (PRES) is suspected	If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If the diagnosis of PRES is excluded, carfilzomib administration may resume at same dose, if clinically appropriate.

Carfilzomib Toxicities	Dosing Modifications
If thrombotic microangiopathy (TTP/HUS) is suspected	Hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. *If TMA is confirmed and related to carfilzomib,* permanently discontinue carfilzomib. *If the diagnosis is excluded,* carfilzomib can be restarted at the previous dose. If the condition recurs, permanently discontinue carfilzomib.
Hepatic Impairment: Mild to moderate liver dysfunction: defined as 2 consecutive values, at least 28 days apart, of: (1) total bilirubin (> 33% direct) > 1x ULN to < 3x ULN OR (2) an elevation of AST and/or ALT with normal bilirubin Grade 3 elevation in ALT and/or AST (> 5x ULN) Grade 3 elevation in total bilirubin Drug-induced hepatotoxicity (attributable to carfilzomib)	 25% dose reduction. Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded. Hold carfilzomib until resolution to baseline. Monitor any abnormality weekly. Resume carfilzomib with a 25% dose reduction if drug-induced hepatotoxicity is excluded. Hold carfilzomib until resolution to baseline. Monitor total bilirubin and direct bilirubin weekly. Upon resolution of total bilirubin to normal, resume carfilzomib dosing with a 25% dose reduction if drug-induced hepatotoxicity is excluded. **Discontinue carfilzomib**
Thrombotic Microangiopathy (TMA)	If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted.

3.3.4 Dose Reductions: Extended Dosing Phases I and II

	Lenalidomide
Baseline dose	10 mg daily on Days 1-21 of 28 day cycle
One level dose reduction	5 mg daily on Days 1-21 of 28 day cycle

3.3.5 Hematologic Toxicity: Extended Dosing Phases I and II

3.3.5.1 On day 1 (or within 7 days prior to day 1) of every third cycle during extension phase, patients must meet the following criteria or dose modify based on dose reductions in table 3.3.4:

- ANC $\geq 1.0 \times 10^9$ /L

- Platelet count >50 x 10^9/L during cycles 9 and beyond

If these conditions are not met on Day 1 of every third cycle, treatment will not be initiated until the toxicity has resolved or returned to baseline. If there is no resolution after 2 weeks of withholding treatment or up to 3 weeks for infection related treatment, the subject will go off therapy.

3.3.5.2 If a patient develops thrombocytopenia or neutropenia during the cycle, then the following actions would take place (see Thrombocytopenia/Neutropenia table below).

Thrombocytopenia	**Lenalidomide**
Fall to < 25 x 10^9/L	Hold Lenalidomide, follow CBC weekly. Hold prophylactic anti-coagulation.
Return to ≥ 25 x 10^9/L	Resume lenalidomide at next dose reduction if deemed drug related
Subsequent fall to < 25 x 10^9/L	Hold Lenalidomide. Hold prophylactic anti-coagulation
Return to ≥ 25 x 10^9/L	Patient will go off therapy if deemed drug related

Neutropenia (Absolute Neutrophil Count)	**Lenalidomide**
Falls to < 0.5 x 10^9/L or to < 1.0 x 109/L with fever	Hold Lenalidomide. Add filgrastim if Grade 3 with fever (single temperature of 38.3o or sustained temperature of 38o for > 1 hour) or Grade 4. Follow CBC weekly
Returns to ≥ 1.0 x 10^9/L	Resume Lenalidomide at next dose reduction.
Subsequent drop to < 0.5 x 10^9/L or to < 1.0 x 109/L with fever	Hold Lenalidomide. Add filgrastim if Grade 3 with fever or Grade 4. Follow CBC weekly
Returns to ≥ 1.0 x 10^9/L	Patient will go off therapy if deemed drug related

3.3.6 Non-Hematologic Toxicity- Extended Dosing Phase

3.3.6.1 Toxicity ≥ grade 3 will require study drug to be held until resolved to ≤ Grade 1 or baseline unless specified below.

3.3.6.2 Once toxicity has resolved ≤ grade 1 or baseline, subsequent doses will be reduced at next dose level (according to table in Section **3.3.4**) if the adverse event was deemed to be treatment related by the PI. If the adverse event was deemed to be unrelated to treatment, the patient may continue the full dose. In the case of renally adjusted doses, dosing modifications are made according to table below.

3.3.6.3 Readily reversible electrolyte and metabolic abnormalities or infections controlled by appropriate therapy are exempt.

Common Lenalidomide Toxicities	Dosing Modifications
Non-Blistering Rash	• If Grade 3, hold lenalidomide dose and restart at next dose reduction once rash improves to ≤ Grade 1 • If Grade 4, discontinue lenalidomide and remove patient from therapy
Blistering Rash (Any Grade)	Discontinue lenalidomide and remove patient from therapy
Venous thrombosis/embolism	Hold lenalidomide and start therapeutic anticoagulation. Restart lenalidomide at investigator's discretion at current dose level.
Renal Dysfunction: CrCl based on Cockcroft-Gault. (NOTE: Alternatively, MDRD or CKD-epi formulas may be used to estimate eGFR as more accurate indictors of renal dysfunction than CrCl in discrepant cases.)	• CrCl 31-50 ml/min – Dose reduce lenalidomide to 10 mg daily from Days 1-21 • CrCl ≤30 mL/min (not requiring dialysis) – Dose reduce Lenalidomide to 15 mg every 48 hours and see carfilzomib dosing below. • CrCl ≤30 mL/min (requiring dialysis) – Decrease Lenalidomide to 5 mg daily and on dialysis days dose lenalidomide after dialysis.

3.3.7 Monitoring

3.3.7.1 Patients may be observed in the hospital for administration of cycle 1 Days 1 and 2 of therapy (at the discretion of the investigator).

3.3.7.2 Routine labs (cbc w/differential, acute care, mineral, hepatic panels, uric acid and LDH) will be performed on Day 1, 2, 8, 15, and 22 of cycle 1 and Day 1 of each cycle during cycles 2-8 and on Day 1 (or within 7 days prior to day 1) of every third cycle during extension phases I and II.

3.3.7.3 Myeloma tests include serum protein electrophoresis, serum immunofixation, serum free light chains, quantitative immunoglobulins, beta-2 microglobulin and will be performed at baseline and Day 1 of each cycle and on Day 1 (or within 7 days prior to day 1) of every third cycle during extension phase I and II. Subsequent serum immunofixation will only be performed on those patients clinically indicated.

3.3.7.4 Random urine sample for protein electrophoresis (UPEP) and immunofixation to assess for monoclonal protein in the urine (Bence-Jones proteinuria) to be performed at baseline, day 1 of each cycle 1-8, and day 1(or within 7 days prior to day 1) of every third cycle during extension phase I and II. In patients whose measurable disease is best determined by measuring Bence- Jones protein quantification, a 24-hour UPEP will be performed at baseline, day 1 of each cycle 1-8, and day 1 (or within 7 days prior to day 1) of every third cycle during extension phase I and II. Otherwise, 24-hr UPEP Bence-Jones quantification will be estimated from random UPEP specimens performed at baseline, day 1 of each cycle 1-8, and day 1 (or within 7 days prior to day 1) of every third cycle during extension phase [46].

3.3.7.5 Patients will have clinic visits with H&P or standard progress notes assessing for toxicity/side effects on Day 1, 2, 8, 15, and 22 of cycle 1 and Day 1 (or within 7 days prior to day 1) of each cycle during cycles 2-8 and on Day 1 (or within 7 days prior to day 1) of every third cycle during extension phases I and II. May be delayed up to 7 days per PI discretion for clinical or logistical reasons.

3.3.7.6 Additional laboratory studies and clinic visits will be performed if clinically indicated.

3.3.7.7 FDG-PET scan and/or DW-MRI will be performed on patients at baseline, during cycles 1-8 if patient obtains CR or at the end of cycle 8 if no CR is achieved, during cycles 9-20 if patient obtains CR or at the end of cycle 20 if no CR is achieved, and during cycle 21 and beyond if patient obtains CR or at treatment termination. During extension phase lenalidomide, FDG-PET scans and/or DW-MRIs are optional for those patients that are MRD negative at the end of cycle 8 regardless of response. At PI discretion, patient may be asked to have an additional PET-CT and/or DW-MRI at progression.

3.3.7.8 During lenalidomide extension phases I and II, FCBP patients will still be required to have pregnancy testing as outlined in **APPENDIX B**. Local treating physicians will be required to submit results to NIH clinical center for review.

3.4 STUDY CALENDAR

Test/Procedure	Screening	Baseline	Induction Treatment [q]						Extended Treatment (Phases I and II)[q]		End of Treatment[r] and Follow-Up	Disease Progression at any Time Point[k]
			Cycle 1				Cycle 2-8					
			Day 1	Day 8	Day 15	Day 22	Day 1	CR Achieved/ End of Cycle 8[l, m, n]	Day 1 of every third cycle from cycle 9 and beyond [p]	Phase I-CR Achieved (Cycle 9-20)/ End of Cycle 20 and Phase II-CR achieved (Cycle 21-32)/ Treatment termination [l, m, n, p]	Every 3-6 months[j, m, q]	
Medical Record Review	x										x	
H&P/Clinic Visit	x		x	x	x	x	x		x			
ECOG	x						x		x			
Informed Consent	x											
Routine Labs[a]	x		x	x	x	x	x		x		x	
Urine for UPEP and IFE [l]	x[l]		x				x[l]	x[l]	x[l]	x[l]		
Viral Studies[b]	x											
Register for RevAssist		x										
Pregnancy Test[c]	x[c]		x[d]	x[e]	x[e]	x[e]	x[c]		x[c,e]	x[e]	x[e]	
Myeloma tests[f]	x						x		x	x[o]	x	
Research Blood/Urine *		x		x	x		x	x	x	x	x	x
Bone Marrow/Aspirate	x[g]							x[i, n]		x[i, n]	x[i]	x
Skeletal Survey	x											
FDG PET-CT		x						x[m]		x[m]	x	x
MRI of spine	x[s]											
Diffusion Weighted MRI		x						x[m]		x[m]	x[m]	x[m]
Echocardiogram, BNP and Troponin		x										
Adverse Events			x	→	→	→	→	→	→	→	→	
12 lead EKG	x											

NOTE: All assessments are pre-dose on the day indicated, unless otherwise described below. After initiation of treatment, variations of +/- 3-14 days of scheduled visits are permitted, as noted (see also footnote q). For patients who choose to undergo stem cell harvest, next cycle may be delayed for up to 5 weeks. Refer to Section **5.1** for specific details on research samples and imaging correlates to be collected. *See Section **5**, Correlative Studies for Research, for additional information on the research blood, urine, and bone marrow sampling. Note, that any missed research blood/urine tests or surveys will not be considered protocol deviations.

a. Routine tests include CBC with differential, reticulocyte count, Acute Care (sodium, potassium, chloride, CO2, glucose, BUN, creatinine), Mineral (serum calcium, phosphate, magnesium and albumin) and Hepatic (alkaline phosphatase, ALT, AST, total and direct bilirubin) Panels, uric acid, eGFR determination, and LDH. NOTE: PT and PTT will only be performed at baseline.

b. Viral studies include Hep B surface antigen and Hep C antibody. If Hep C antibody positive, Hep C RNA PCR will be performed

c. Pregnancy tests (urine or serum) for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female 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). During extension phase, FCBP patients will have pregnancy tests per footnote "e". Local treating physicians will be required to submit results to NIH Clinical Center for review.

d. Pregnancy tests (urine or serum) must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days).

e. FCBP with regular or no menstruation must have a pregnancy test (serum or urine) weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test (serum or urine) weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see **APPENDIX B**).

f. Myeloma tests include serum protein electrophoresis, serum immunofixation, urine electrophoresis, urine immunofixation, serum free light chains, quantitative immunoglobulins, beta-2 microglobulin and will be performed at baseline and Day 1 of each cycle. Subsequent serum immunofixation, urine immunofixation, and urine electrophoresis will only be performed on those patients clinically indicated.

g. Baseline bone marrow aspiration and biopsy will be sent to Dept. of Pathology, flow cytometry, FISH/cytogenetics, CD 138 sorting/GEP/storage (Young Lab) and heavy/light chain immunoglobulin rearrangement (optional) and/or NRAS/KRAS mutations in Molecular Pathology (optional). For screening eligibility purposes, an outside bone marrow may be used in which case a baseline at the NIH will also be performed. **Note:** As of February 6, 2023, all participants have completed the maintainance phase (C32) thus bone marrow and peripheral blood research samples will be sent to Ryan Young's lab on a case to case basis.

h. FOOTNOTE NO LONGER APPLIES/DELETED IN AMENDMENT M (version date 07/20/2018). PREVIOUS TEXT: Optional Cycle 1 Day 2 bone marrow aspirate alone sent for CD138 sorting (GEP studies and microenvironment studies). NOTE: This no longer in effect with Amendment H (version date 06/30/2017).

i. Bone marrow aspirate and biopsy can be performed +/- 21 days of intended cycle day. Bone marrow aspirate and biopsy will be sent to Hematology Section, Department of Lab Medicine (DLM), flow cytometry (bone marrow immunophenotyping of plasma cells), CD 138 sorting/GEP/storage, and +/- heavy/light chain immunoglobulin rearrangement and/or NRAS/KRAS mutations in Molecular Pathology (optional). In follow up period, PET/CTs will be done approximately annually.

j. At minimum, follow-up will be every 3-6 months until progression of disease, or death. Patients may be followed at more frequent time intervals if clinically indicated, i.e. following post-therapy toxicity. Patients who have progressive disease while on study will be followed with restaging scans and laboratory tests as clinically indicated. Patients who are taken off treatment will continue to be followed for survival by phone or clinic visit. Patients who finish all 32 cycles of treatment will be followed at least every 6 months by clinic visit with laboratory evaluation and by bone marrow biopsy yearly at the discretion of the investigator. Of note, patients who do not progress, but decide to

continue or resume therapy at an outside facility, may be followed by clinical and laboratory examination every 3-6 months. Alternatively, this data may be captured by investigator-patient or investigator-physician phone or email communication if the required examinations have been performed at the outside facility.

k. At disease progression, marrow and FDG-PET/CT are optional.

l. Urine for protein electrophoresis (UPEP) and immunofixation to assess for monoclonal protein in the urine (Bence-Jones proteinuria) at screening, day 1 of each cycle during cycles 1-8, day 1 of (or within 7 days prior to day 1) every third cycle during cycles 9-32, and at treatment termination. In patients whose measurable disease is best determined by measuring Bence- Jones protein quantification, a 24 hour UPEP will be performed at baseline, day 1 of each cycle 1-8, and day 1 (or within 7 days prior to day 1) of every third cycle during extension phase I and II. Otherwise, 24-hr UPEP Bence-Jones quantification will be estimated from random UPEP specimens performed at baseline, day 1 of each cycle 1-8, and day 1 (or within 7 days prior to day 1) of every third cycle during extension phase[46].

m. FDG-PET scan will be performed on patients at baseline, during cycles 1-8 if patient achieves CR and/or at the end of cycle 8 if no CR is achieved, during cycles 9-20 (extended dosing phase I) if patient achieves CR and/or at the end of cycle 20 if no CR is achieved, and during cycles 21-32 (extended dosing phase II) if CR is achieved or at treatment termination. FDG-PET scan can be performed +/- 21 days of intended cycle day. For patients who are on extended dosing with lenalidomide and are found to be negative by immunohistochemistry and flow cytometry of the bone marrow (MRD negative), clearance of abnormal protein in blood and/or urine does not mandate a repeated bone marrow and the results will be interpreted as complete response. However, a bone marrow will be repeated at the discretion of investigator. Diffusion weighted MRI (DW-MRI) will also be performed at the discretion of the PI. DW-MRI will be performed by standard techniques in the NCI Molecular Imaging Program. In follow up, PET/CTs and DW-MRIs will be done approximately annually, if feasible (i.e., missed scans will not be considered protocol deviations). Note: DW-MRIs are optional after Cycle 8.

n. Bone marrow biopsy and aspirate will be performed on patients at baseline, during cycles 1-8 if patient achieves CR or at the end of cycle 8 if no CR is achieved, during cycles 9-20 (extended dosing phase I) if patient achieves CR or at the end of cycle 20 if no CR is achieved, and during cycles 21-32 (extended dosing phase II) if CR is not achieved or at treatment termination. Bone marrow aspirate and biopsy can be performed +/- 21 days of intended cycle day.

o. Repeat myeloma tests at treatment termination.

p. Within 7 days prior to D1 of each cycle.

q. After initiation of treatment, visits may be adjusted per PI discretion for logistical or administrative reasons (e.g. holidays, bad weather, etc.); this may include skipped doses of lenalidomide. For cycles 2-8, the preferred adjustment is -1/+3-day with no more than 2 missed doses of lenalidomide. For cycles 9-forward, the preferred adjustment is -1/+7 days. For follow-up period may be adjusted from every 3-6 months to up to 6 months (+6 months) at the discretion of the PI

r. End of treatment visit will occur approximately 30 days (+/- 7 days) after the last dose of study drug. If the patient cannot return to the Clinical Center for this visit, a request will be made to collect required clinical labs (specify as needed) from a local physician or laboratory. If this is not possible, patients may be assessed by telephone for symptoms.

s. At the discretion of the Principal Investigator, PET/CT may replace MRI in patients who have a contraindication to MRI.

3.5 COST AND COMPENSATION

3.5.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.5.2 Compensation

Participants will not be compensated on this study.

3.5.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days (+/- 7 days) following the last dose of study therapy.

3.6.1 Criteria for removal from protocol therapy

- Patients with medically concerning grade 3 or 4 adverse events related to drug therapy may be taken off therapy at the discretion of the principal investigator.
- Patients require more than 2 dose reductions of carfilzomib.
- Toxicity has not resolved after 2 weeks of withholding treatment or up to 3 weeks for infection related treatment
- Grade 3 non-blistering rash or blistering rash of any grade
- Grade 3 neuropathy
- Grade 3 hypersensitivity reaction
- Diagnosis of posterior reversible encephalopathy (PRES) or thrombotic microangiopathy (TMA)
- Patient completes the protocol (as outlined in Section **3.2**)
- Progression of disease
- Patient chooses to go off therapy
- The principal investigator may remove patient from protocol therapy if deemed necessary due to medical conditions, compliance, etc.
- Patient becomes pregnant.

3.6.2 Off-Study Criteria

- Patient requests to be withdrawn from study

- Death
- Physician's determination that withdrawal is in the patient's best interest.
- Patients who receive non-protocol therapy for progression to symptomatic myeloma may remain on study for evaluation (by phone, email, or clinic visit) of survival per study schedule at the discretion of the investigator.
- Patients who have not progressed but choose to continue lenalidomide maintenance beyond 32 cycles at an outside facility may stay on study at the discretion of the investigator.
- Permanent loss of capacity to give consent
- Screen failure
- Lost to follow up

3.6.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for three (3) consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within five (5) business days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS/MEASURES AND CONSIDERATIONS

4.1 TUMOR LYSIS SYNDROME

4.1.1 Hydration and Fluid Monitoring Guidelines

a. Oral hydration: All subjects must be well hydrated (i.e., volume replete). Begin oral hydration equal to approximately 30 mL/kg/day (~6–8 cups of liquid per day), starting 48 hours prior to the planned first dose of carfilzomib.

b. IV hydration: Adequate hydration is required prior to dosing in Cycle 1, especially for patients at high risk of tumor lysis syndrome or renal toxicity. The recommended hydration includes both oral fluids (30 ml per kg at least 48 hours before Cycle 1, Day 1) and intravenous fluids (250 ml to 500 ml of appropriate intravenous fluid prior to each dose in Cycle 1). If needed, given an additional 250 to 500ml following carfilzomib administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor patients for evidence of volume overload and adjust hydration to

individual patient needs, especially in patients with or at risk for cardiac failure. Total volume will be determined at the discretion of clinician and volume status of patient.

c. In subjects considered to be still at risk for TLS at completion of Cycle 1, hydration should be continued into subsequent cycles if clinically indicated.

4.1.2 Laboratory Monitoring

a. Appropriate chemistries, including creatinine, and complete blood counts (CBC) with platelet count should be obtained and reviewed prior to carfilzomib dosing. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose.

b. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose

4.1.3 Clinical Monitoring

a. Signs and symptoms indicative of TLS, such as fevers, chills/rigors, dyspnea, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output.

b. Patients will be admitted to the inpatient hospital and observed while receiving Cycle 1 Days 1 and 2 of therapy.

4.1.4 Management

a. If TLS occurs, cardiac rhythm, fluid, and serial laboratory monitoring should be instituted. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer therapeutic and supportive care, including dialysis, as clinically indicated.

b. All cases of TLS must be reported to Amgen as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event.

4.1.5 Optional medication for high risk TLS patients:

a. Allopurinol is optional and will be prescribed at the Investigator's discretion. These subjects may receive allopurinol 300 mg PO BID (Cycle 1 Day -2, Day -1), continuing for 2 days after Cycle 1 Day 1 (total of 4 days), then reduce dose to 300 mg PO QD, continuing through Day 17 of Cycle 1. Allopurinol dose should be adjusted according to the package insert. Subjects who do not tolerate allopurinol should be discussed with the Lead Principal Investigator.

4.2 TRANSFUSIONS/GROWTH FACTORS

Subjects may receive RBC or platelet transfusions if clinically indicated.

Colony-stimulating factors may be used if neutropenia occurs but should not be given prophylactically.

4.3 ANTI-COAGULATION

Oral Aspirin 81 mg or 325 mg or suitable alternative anti-coagulation for thrombotic prophylaxis every day for the duration of their participation in the study. Anti-Xa levels will need to be followed in those patients with eGFR≤30 ml/min and receiving enoxaparin. In general,

temporarily holding of prophylactic or treatment doses (for venous thrombo-embolism) anti-coagulation with either aspirin or enoxaparin peri-procedurally (e.g., for bone marrow biopsies) is not required. However, in rare cases, the clinician may hold when clinically indicated.

4.4 HSV AND VSV PROPHYLAXIS

Oral Valacyclovir of 500 mg daily or oral Acyclovir of 800 mg BID throughout all cycles in which carfilzomib is given.

4.5 ANTIBIOTIC PROPHYLAXIS

Patients at risk for developing infections will be offered antibiotic prophylaxis. Risk assessment will be performed by clinical investigator. For instance, diabetic patients or patients taking chronic steroids will be offered Bactrim prophylaxis (or similar agents) to avoid risk of PCP infection.

4.6 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Patients on this study will be monitored for any new or worsening neurologic, cognitive or behavioral signs and symptoms that may be suggestive of PML as part of the differential diagnosis of central nervous system disorders. If PML is suspected, withhold administration of carfilzomib; subjects should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Carfilzomib should be discontinued if PML diagnosis is confirmed.

4.7 HEPATITIS B VIRUS (HBV) REACTIVATION

Active HBV is an exclusion criterion for this study. However, some patients who are carriers for HBV will be allowed on study. For subjects who are carriers of HBV, prophylaxis with antivirals should be considered. Carriers of HBV who require treatment with carfilzomib should be closely monitored for signs and symptoms of active HBV infection throughout and following the end of treatment with carfilzomib. For subjects with active HBV reactivation, carfilzomib should be withheld until infection is adequately controlled.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

	Baseline	**During Cycle 2-8 or End of Cycle 8***	**During Extended Dosing Phases of Cycles 9-20/ End of Cycle 20 OR Cycles 21-32/End of Cycle 32/ End of Treatment#**	**Follow-Up Period after 32 cycles of maintenance every 3-6 months^**	**Disease Progression**
Pathology/IHC	X	X	X	X	X
Multiparametric Flow Cytometry	X	X	X	X	X
FISH/Cytogenetics	X				X
Molecular pathology for light or heavy chain immunoglobulin rearrangement and/or KRas and NRas mutation analysis **(NOTE: Not to be performed as of Amendment H (version date 06/30/2017))**	X	X (optional)	X (optional)		X
CD138+ sorting/Gene expression profiling/ microenvironment	X	X	X	X	X
Other research lab as below, including Next Generation Sequencing	X	X	X	X	X
Storage	X	X	X	X	X
*During Cycle 2-8 if CR achieved or End of Cycle 8 if no CR is achieved #During Extended Dosing Phases (Phase I and II) if CR achieved during cycles 9-20/ End of cycle 20 and if CR achieved during cycles 21-32/End of Cycle 32 (or end of treatment). ^ During the Follow-Up Period, any missed research blood/urine tests or surveys will not be considered protocol deviations.					

Note: Biospecimen collection directly from participants is completed; analyses are undergoing.

5.1.1 Bone Marrow and peripheral blood

Sampling Time Points of Bone Marrow correlative studies

Although specified types of tubes are listed below, based on availability and investigator discretion, tube types may be substituted for any of the assays to be performed.

Effective with Amendment G (version date 07/20/2015), bone marrow aspirate and biopsy will be obtained for research studies at the discretion of the PI.

a. During extension phase lenalidomide, bone marrow biopsy and aspirates are optional for those patients that are MRD negative at the end of cycle 8 regardless of response.

b. Patients may be asked to undergo bone marrow procedure with aspiration and core biopsy at progression of disease at the discretion of the PI.

c. Collection of bone marrow, sorting of bone marrow and storage of bone marrow samples is outlined in **APPENDIX C** and Section **5.2.1**.

d. Correlative studies associated with bone marrow specimen will be performed and related to clinical outcome if the results of the study indicate a clinical or translational rationale for analyzing the samples. Such studies may include but are not limited to the following:

i. Pathology/Immunohistochemistry: Bone marrow biopsy and aspirate will be sent to Clinical Center Department of Laboratory Medicine, Hematology Section for morphological evaluation by Irina Maric, MD and Clinical Center Hematology Staff. Immunohistochemical staining will be performed under the direction of Irina Maric, MD. Plasma cell burden will be assessed using immunohistochemistry markers such as CD 138, light chains, CD56 etc. Plasma cells and microenvironment interactions will also be assessed using various immunohistochemistry markers for osteoblasts, osteoclasts, stromal cells and proteasomes.

ii. Minimal Residual Disease:

- Flow cytometry: Immunophenotyping of aberrant plasma cells by flow cytometry currently involves, but is not limited to, the use of the following reagents: CD138, CD19, CD45, CD38, and CD56. Characteristic changes in immunophenotypically abnormal plasma cells (CD138 positive) include but are not limited to absent CD19 and CD45, decreased CD38, and increased CD56. These studies will be performed under the direction of Hao-Wei Wang of the flow cytometry unit in the NCI Laboratory of Pathology.

iii. FISH and cytogenetics: Interphase FISH/cytogenetics had been performed on patients enrolled in this protocol in the NCI Laboratory of Pathology Clinical Cytogenetics Unit. As of amendment H (version date 06/30/2017), FISH/cytogenetic information may be derived from the patient's outside records or performed on baseline bone marrow samples at a third-party testing laboratory per the CC DLM clinical laboratory protocol/procedure which currently is done at the Mayo laboratories, Test ID: PCPDF, Plasma Cell Proliferative Disorder (PCPD).

iv. Cell Sorting, GEP profiling, whole exome sequencing, microRNA analysis and microenvironment interactions - Marrow aspirate will be sent to the lab of the Dr. Ryan Young (Building 10/4N106) in the Department of Laboratory Medicine and sorted into CD 138 + and CD 138 – fractions. Dr. Young and staff will also perform the below assays for unsorted bone marrow aspirate for VDJ sequencing and assessment of MRD negativity. **Note:** As of February 6, 2023, all participants have completed the maintainance phase (C32) thus bone marrow and peripheral blood research samples will be sent to Ryan Young's lab on a case to case basis.

- GEP profiling targeted exome sequencing, and VDJ sequencing for MRD assessment: Bone marrow aspirates will be collected and sent to the Young Lab after 8 cycles of induction or CR, after 20 and 32 cycles of treatment and at annual follow-up milestones where BM aspirates are collected (if the samples were collected from the patients.) At baseline: CD138+ plasma cells will be purified from bone marrow aspirates harvested. Baseline CD138+ cells will be sent for VDJ sequencing and to University of Miami (Dr. Ola Landgren) for targeted/whole exome sequencing and molecular expression analyses (depending on resources) in a coded, linked manner. At subsequent time points, once patient is in CR, plasma cells will not be purified and aspirates will be viably frozen. Samples will be sent out in batches. Of note, some samples may be sent to FDA/OHOP for next generation sequencing, see below.
- Bone marrow, blood and urine samples, and associated clinical lab data will be sent to Adaptive Biotechnologies Corp. for deep sequencing of the VDJ sequence. Samples and data will be submitted to Adaptive Biotechnologies Corp. without any personal identifiers.
- CD 138- fractions from baseline samples will be analyzed for microenvironment interactions such as cytokine profiling, miRNAs, etc. in the Young Lab. A fraction of CD138- cells will also be cultured to isolate bone marrow stromal cells for further analyses. At the same time points, one 6 ml EDTA tube of peripheral blood will be collected for parallel analysis.
- Both fractions will be collected, batched, and entered into a biobank. See Section **5.3** for storage of bone marrow biobank. As of Amendment H (version date 06/30/2017), As of Amendment version date 01/12/21, aspirate samples will be stored in DLM under Dr. Young.
- Aspirate samples may also undergo identification of downstream signaling targets, proteasome activity, and ubiquitination pathways on cell lysate or marrow aspirate.

v. Additional molecular profiling including DNA-, RNA- and protein-based assays in bone marrow, blood, and urine samples will be performed. The purpose of these assays will be to further characterize underlying biology and correlate with clinical outcomes in an exploratory manner. These are not limited to, but include the following.

- Next Generation Sequencing (NGS) collaboration with Office of Hematology and Oncology Products (OHOP) FDA

This study will be involved in the multi-protocol CCR collaborations with OHOP/FDA in terms of the translational and correlative aspects utilizing OHOP's "wet lab" to perform NGS assays on various human samples enrolled on a variety of CCR clinical trials. The transfer of samples will be performed under a CCR "umbrella" MTA. The samples will be locally biobanked in the BPC (Figg Lab)

and batched at the NIH until time for shipment, at which time, the samples will be sent to:

ATTN: Elliot Rosen, Ph.D.
DBRR III/OBP/OPQ/CDER
Food and Drug Administration
10903 New Hampshire Ave,
Bldg. 52/72, Room 2248,
Silver Spring, MD 20993
Tel: 240-402-7353
Email: Elliot.Rosen@fda.hhs.gov

The correlative NGS assays to be performed will be dependent on final agreement in investigating mutually important questions of interest with our collaborators. These include but are not limited to all or some of the following but are all optional:

1. T-cell receptor repertoire (immunoseq): More recently research in the literature has shown that patients most likely to benefit from immunotherapies are those who are found to have anti-tumor T cell clonality. Lenalidomide is an immunomodulatory and therefore it is important to analyze this along with immune subsets below in SMM. NGS DNAseq will be used to analyze the VDJ sequence of T-cells to determine clonality. Input source may be PBMC or whole blood and approximately 2 ug of input gDNA will be needed which will amount to a whole blood collection of two 10 ml EDTA tubes. Collection time points include the following milestones, baseline, C8 or CR, 1 year and 2 years.
2. Germline single nucleotide polymorphisms (SNP) and copy number variations (CNV) DNAseq: Whole exome or genome sequencing will be performed on peripheral blood to determine baseline germline SNPs and CNVs. Whole blood (one 10 mL EDTA tube) sample will be collected at baseline for germline DNA extraction. This DNA will be used to analyze and compare germline vs. somatic/tumor genetic alterations based on sequence data. Furthermore, germline normal polymorphic variation will be analyzed as genome-wide association study (GWAS) to determine whether certain normal variations predispose patients with treated SMM to progress to biochemical or overt symptomatic disease. Additionally, these germline variations may be analyzed for association with treatment related adverse events.
3. ctDNA: Targeted DNAseq will be performed on ctDNA for assessment of minimal residual disease (MRD). In addition to the VDJ targeted commercial assay to determine presence of the malignant clone, the library will also include other known recurrent genetic aberrations. Approximately 45% of myeloma patients have hyperdiploidy of one of the odd numbered chromosomes, the other 45% have specific translocations/deletions, well characterized, including translocations of 6;14, 11;14, 4;14, 14;16, 16;18, 17p del, and cMYC. Therefore, the assay will focus on both VDJ as with other hematologic malignancies and recurrent genetic alterations similar to the

approach used in solid malignancies. Blood collection will involve two 10 mL EDTA tubes, alternatively, Streck tubes may be used if processing of the sample will be delayed by more than 2 hours.

4. Gene expression profiling: RNAseq will be performed on CD138+ myeloma cells and correlated with DNAseq results. Additionally, peripheral blood/PBMC will analyzed for immune related signatures. One 10 mL EDTA tube will be used for this purpose.

vi. Immune subset analysis

Bone marrow and PBMCs will be processed, stored, and assessed by the Developmental Therapeutics Branch (DTB) Lab using multiparameter flow cytometry for immune subsets including but not necessarily limited to Tregs, MDSC subsets, monocyte subsets, CD8+ T-cells and CD4+Foxp3- T-cells. Assessment will include functional markers, i.e. PD-1, Tim-3, CTLA-4 and/or CD40.

- PBMC collection of specimen(s): Two 8-10 ml EDTA (purple top) or BD Vacutainer Cell Preparation Tubes (CPB; blue and black tiger top) will be collected from each patient. Immediately after collection, mix the blood sample by gentle inversion several times. The date and exact time of each blood draw should be recorded on the tube.
- Bone marrow collection of specimens: 1 ml of bone marrow will be collected from each patient

Collection Time points

- Blood: Baseline, C3D1pre, post C8 or CR, post 1 year and post 2 years
- Bone marrow: Baseline, post C8 or CR, post 1 year and post 2 years

Notification and Handling:

As soon as possible after the patient is scheduled please send email notification to DTB lab (Sunmin Lee at leesun@mail.nih.gov and/or Min-Jung Lee at leemin@mail.nih.gov) and call the lab at 240-760-6330 when the sample is drawn and a lab member will come for immediate pick up.

5.1.2 Research Blood/Serum and Urine

5.1.2.1 At any given time, up to 100cc of peripheral blood will be collected. The amount of blood collected will be dictated by the number of experiments to be performed, and by the patient's peripheral blood count. Typical time points include:

- Baseline
- Days 8 and 15 of Cycle 1
- Day 1 of every cycle during cycles 2-8; and if patient achieves CR or at the end of cycle 8 if no CR is achieved
- Day 1(or within 7 days prior to day 1) of every third cycle during cycles 9 and beyond during extended dosing phases (I and II), if patient achieves CR or at

the end of cycle 20 if no CR is achieved, during cycles 21-32 if CR is achieved or at treatment termination.

- Every 3-6 months during the post-maintenance follow-up period
- Disease Progression: at any time point if the patient has progression of disease

5.1.2.2 The standard number of peripheral blood research tubes drawn for collection and storage at each of the above time points may include but are not limited to the following: one 8 mL serum separator tube (SST), one 10 mL sodium heparin tube (GTT), and one 10 mL EDTA lavender top tube for storage in the Blood Processing Core (BPC) in 10/5A09 (Figg Lab) for biobanking. Additionally, up to six 10 ml EDTA tubes may be collected for various experiments to be performed with FDA collaborators, see below and one 6 mL EDTA lavender top tube for analysis and storage in the Young Lab.

5.1.2.3 At any given time, approximately 45 mL of urine will be collected into a standard urine collection cup and sent for analysis and storage at each of the above time points. Typical time points include:

- Baseline
- Day 8 and 15 of Cycle 1
- Day 1 of every cycle during cycles 2-8
- Day 1 (or within 7 days prior to day 1) of every third cycle during cycles 9 and beyond during extended dosing phases (I and II) if patient achieves CR or at the end of cycle 20 if no CR is achieved, during cycles 21-32 if CR is achieved or at treatment termination.
- Disease Progression: at any time point if the patient has progression of disease.

NOTE: The amount of urine collected will be dictated by the number of experiments to be performed.

5.1.2.4 Collection and storage of peripheral blood and urine outlined in **APPENDIX D**. Sample Requirements and Handling: The date and exact time of each blood draw should be recorded on the sample tube. Serum samples should be kept at room temperature for 30-60min prior to being refrigerated.

5.1.2.5 Peripheral blood and/or urine samples from patients will be analyzed for potential serum or urine biomarkers as well as drug concentrations, and correlated to clinical outcomes if the results of the study indicate a clinical or translational rationale for analyzing the samples. Such biomarkers may include but are not limited to:

- Peripheral blood flow cytometry assessing for circulating plasma cells under the direction of Hao-Wei Wang, MD.
- Subunit profiling and activity of circulating proteasomes by enzyme-like immunosorbent assay
- Apoptosis assays pre- and post-carfilzomib to identify necrotic or late stage apoptotic cells
- Immunolocalization studies

- Markers of bone turnover and disease activity
- Peripheral blood will be assessed for immune cell populations including, but not limited to T cells (CD4 and CD8), LGL, and NK cells using flow cytometry.
- Blood and urine samples and associated clinical lab data will be sent to Adaptive Biotechnologies Corp for deep sequencing of the VDJ sequence.

5.1.3 Imaging – FDG-PET/CT

5.1.3.1 Schedule

FDG-PET scan will be performed on patients at baseline, during cycles 1-8 if patient obtains CR or at the end of cycle 8 if no CR obtained, during cycles 9-20 if patient obtains CR or at the end of cycle 20 if no CR obtained, during cycles 21-32 if patient obtains CR or at treatment termination. During extension phase lenalidomide, FDG-PET scans are optional for those patients that are MRD negative at the end of cycle 8 regardless of response. At PI discretion, patient may be asked to have an additional PET-CT at progression.

5.1.3.2 Procedures

Prior to ^{18}F-FDG PET/CT imaging, the subject will have fasted and not received any sugar containing substance (i.e., glucose, sucrose, dextrose) for 4-6 hours. Subjects will be encouraged to drink water during this period to reduce radiation dose to the kidneys and will be asked to void prior to ^{18}F-FDG injection.

Women of childbearing potential will have a documented report of negative pregnancy test from the CC or another accredited lab performed on the day of the scan or the day before the scan.

^{18}F-FDG, [18F]-fluorodeoxyglucose is an FDA approved radiopharmaceutical. Immediately prior to injection, the subject's blood glucose level will be evaluated via finger stick. Non-diabetic subjects with fasting blood glucose levels above 150 mg/dl may be rescheduled at the discretion of the PI. Subjects will be asked to refrain from excessive physical exertion for the 24 hours prior to injection.

Patients will report to the NCI clinic on the day of the F-18 PET/CT scan and peripheral venous access will be obtained (most commonly via IV in the antecubital fossa). The ^{18}F-FDG injection procedure will be injected and be followed by a ~20 ml saline (sodium chloride IV infusion 0.9% w/v) flush over a period of ~20 seconds. The injection site will be evaluated pre- and post-administration for any reaction (e.g., bleeding, hematoma, redness, or infection).

Whole body (vertex to toes) static PET/CT imaging will be performed beginning at approximately 1-hour post injection per PET/CT standard operating procedures. The patient will be instructed to maintain good hydration in order to reduce the radiation dose.

5.1.3.3 Location of Scanners to be used for imaging

5.1.4 Patients may be imaged either in the Molecular Imaging Program (MIP) or Nuclear Medicine to allow flexibility in scheduling; whenever possible, the same scanner used at baseline should be used in follow-up. Imaging – DW-MRI

5.1.4.1 Schedule

For newly enrolled patients, whole body DW-MRI scans will be performed on patients at baseline, cycle 4 and if and when patient reaches a PR, CR, and/or PD, and at the end of treatment. During follow-up period, scans may be done at any time point at the discretion of the investigator. We plan to obtain DW-MRI scans on current patients, for whom we may not have a baseline DW-MRI scan, at the same timepoints, as applicable.

5.1.4.2 Procedures

DW-MRI exploits differences in the diffusion of water in various tissues to internal physiology. The image contrast in reflects the difference in rate of diffusion between tissues. All attempts will be made to perform the DW-MRI scans on the same day as PET/CTs, but is not mandatory. For DW-MRI, no external contrast will be used and fasting is not required. Standard clinical operating procedures will be used for image collection. DW-MRI evaluations will be considered purely exploratory.

5.1.4.3 Results

Patients will be given the results of the DW-MRI scans. But given the exploratory and research nature of the scans, these results will not be used for clinical decision-making purposes.

5.1.5 Patient Reported Outcomes

The PROMIS Patient Reported Outcome Measurement Information System (PROMIS®) QoL instrument was administered to all consenting patients who speak English or Spanish until February 1, 2021. This instrument was administered at baseline; at the start of every cycle (cycles 2-8 only); the start of every 3rd cycle (cycles 9-32 only); every 3-6 months thereafter during the follow-up phase; and at the time a patient was taken off treatment. Since the measures have not been validated in other languages, participation in this portion of the study was limited to subjects who speak either English or Spanish. Further, although patients were not given the option to “opt out” of completing PROs, it was not considered a reportable deviation when PROs were not completed or were missed for any reason as this is an exploratory endpoint.

PROMIS is funded by the National Institutes of Health and provides clinicians and researchers access to efficient, precise, valid, and responsive measures of health and well–being in clinical trial patients. The short forms that were implemented in this study involved questions in the domains of physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference, pain intensity, and cognitive function. A computer tablet-based application also exists which can utilize computer adaptive tests (CAT) which can lower patient burden; that is, adapting the template 37 questions presented on the paper short forms based on patient response. The questionnaires took no more than 20 minutes to complete.

As feasible, the PROMIS data may be captured based on this CAT PROMIS tablet application; alternatively, the paper short forms presented in the appendix will be used. Data was secured on the tablet based on 2 passwords. When results are ready for analysis, they will be exported in excel format and submitted for storage in C3D or Labmatrix, as appropriate.

NOTE: As of February 1, 2021 PROMIS surveys are no longer completed.

5.2 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.2.1 Description of the scope of genetic/genomic analysis

Genomic testing will be done as described in Section **0**.

5.2.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described in Sections **5.3.1** and **5.3.2**. In addition, a Certificate of Confidentiality has been obtained for this study.

5.2.3 Management of Results

We plan to contact participantsif a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of secondary findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

Subjects will be contacted at this time with a request to provide a sample to be sent to a CLIA certified laboratory within the NIH or as a send-out test to another CLIA certified lab.

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

5.2.4 Genetic Counseling

If the research findings are verified in the CLIA certified lab, the subject will be referred to a genetic healthcare provider within the NIH for the disclosure of the results. These activities will be funded by the Center for Cancer Research.

5.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.3.1 Procedures for Collecting, Processing, and Storage of Bone Marrow biopsies

- See **APPENDIX C**
- Orders for bone marrow biopsies should be placed in the Clinical Research Information System (Clinical Research Center, NIH, Bethesda, MD).
- Materials for research studies will be documented on form NIH 2803-1. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.
- Bone marrow biopsies will be submitted in native condition to the NIH Clinical Center Department of Laboratory Medicine and handled according to routine procedures for diagnosis. Bone marrow core biopsies will be fixed and paraffin embedded for histological and immunohistochemical analysis and long-term storage. Bone marrow aspirates will be prepared according to routine procedures. Five to ten air-dried aspirate smears will be stored long-term.
- Initial processing of bone marrow aspirates for research will depend on the size of the aspirate. CD138 positive plasma cells will be isolated from a subset of these samples and stored in Young Lab).
- For the purposes of storage, marrow aspirate will be assigned a unique number and

cataloged. Prior to Amendment H (version date 06/12/2017), these research samples were stored in the laboratory of the Lymphoid Malignancies Branch or in a temperature controlled, alarm secured nitrogen tank in the NCI Department of Hematopathology. As of Amendment H (version date 06/12/2017), these samples will be stored in a temperature controlled, alarm secured nitrogen tank/deep freezer in the NIH Department of Laboratory Medicine. For information regarding these samples, please contact Mark Roschewski, M.D. at 240-760-6183 or Ryan Young at240-858-3513.

- Frozen specimens will be wrapped in aluminum foil labeled with the patient's name and accession number, put into a resealable polyethylene freezer bag, and stored in a liquid nitrogen freezer. The liquid nitrogen freezers are monitored daily for temperature variations. A FileMaker Pro database called HP Patient Information and Specimen Inventory is used for tracking the samples.
- The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

5.3.2 Procedures for stored serum, peripheral blood, and urine specimens in the Blood Processing Core:

See **APPENDIX D** for processing of samples

Please e-mail **Blood Processing Core (BPC)** (Dr. Figg's Lab) at NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964. Samples are to be delivered to the Figg Lab (4B11).

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact BPC by e-mail at NCIBloodcore@mail.nih.gov.

- All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined BPC personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.
- Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).
- Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix .

All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

- Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.
- If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested). The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.
- Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of Labmatrix. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.3.3 Samples processing in the Department of Laboratory Medicine and NCI Laboratory of Pathology.

- Biopsy, bone marrow or peripheral blood samples will be obtained from the Hematopathology Section of the NCI Laboratory of Pathology (LP) or the Hematology Section (HS) of the DLM, CC.
- Samples are coded by the LP HS, DLM HS or Young Lab. Tissue sections, or peripheral blood samples will be obtained and stored in the Young lab or LP Proteomics Core lab without any personal identifiers and will be labeled with the anonymous LP HS or DLM HS sample accession ID number.
- The relationship between the accession ID number and the patient clinical information will be stored in a secure database that is maintained and regularly backed up by Drs. Ryan Young, Elaine Jaffe, or Dr. David Levens.
- The Young laboratory or LP Proteomics Core Lab will prepare tissue lysates, RNA and DNA from each sample. Samples, lysates and derived biologic molecules will be stored in Eppendorf tubes marked with the sample accession ID number in locked -80° C freezers in the Young laboratory or LP Proteomics Core Lab.

5.3.4 Protocol Completion & Sample Destruction

Any specimens that are remaining at the completion of the protocol will be stored in the conditions described above.

The principal investigator will record the following:

- Destroyed samples which become unsalvageable because of environmental factors (ex. a broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent.
- Samples lost in transit between facilities or misplaced by a researcher.

- All other problems associated with samples.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events (AEs), including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of the event.

Document AEs from the first study intervention from Study Day 1 through 30 days after the last dose of study drug. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE only if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.1.1 Long-term follow-up data collection

When patients enter the long-term follow-up period, the following data will be collected:

- adverse events related to Carfilzomib
- survival status which will be collected by phone or clinic visit
- additional cancer therapy received

6.1.2 Record Keeping

Complete records must be maintained on each patient; these records will consist of the hospital chart as well as any other outside information obtained from outside laboratories, radiology reports, or physician's records. The primary source documentation will include patient eligibility

data, patient history, flow sheets (including specialty forms for pathology, radiology, or surgery), an off-study summary sheet, and a final assessment by the treating physician.

6.1.3 Forwarding of Patient Data from Other Institutions

Either due to extenuating medical circumstances or for convenience, some patients may elect to have certain routine laboratory studies or protein marker analyses performed at an outside institution between scheduled interval visits to the CRC for this protocol. These results will be forwarded to the Myeloma Research Nurse; the data will be entered into the study database and filed in the medical record. Additional blood or tissue samples drawn on patients enrolled in this protocol between scheduled visits may be forwarded and entered into the database as indicated.

6.2 DATA SHARING PLAN

6.2.1 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

Response assessments will be performed Day 1 of every cycle during Cycles 1-8 and every third cycle during Cycles 9-20: Cycles 9, 12, 15, 18 and every third cycle during Cycles 21-32: Cycles 21, 24, 27, 30 and end of 32. During the follow-up period, response assessments will be done every 3-6 months, unless being primarily followed at outside facility at which time all effort will be made to receive response data at least yearly.

6.3.1 Disease Parameters

- Measurable is defined as any of the following: serum M-protein is ≥ 1 g/dL or "measurable" urine M-spike is ≥ 200 mg/24 hours or serum kappa or lambda FREE light chain of 10 mg/dL along with an abnormal kappa to lambda free light chain ratio.
- The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory disease. When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and do not solely represent monoclonal elevations. 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. The serum FLC assay should be used in assessing response only if the baseline serum and/or urine M proteins are not “measurable” by traditional criteria (serum M protein ≥ 1gm/dL and/or urine M protein ≥ 200 mg/24), and the baseline level of the involved FLC is ≥ 10mg/dL and clonal (abnormal ratio). Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results.
- In order to be classified as a hematologic response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations.
- Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiological 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 PI before removing the patient from the study.

- Appearance of monoclonal or oligoclonal bands that are different from original isotype may not be defined as "relapse from CR". Oftentimes, such bands may indicate fluctuations in immunological parameters that are not reflective of MM disease. In these situations, immunofixation and electrophoresis will be interpreted by the clinician before being labeled as "relapse"[47, 48].
- Random urine specimens will be performed day 1 of each cycle (cycles 1-8) and day 1 (or within 7 days prior to day 1) of every third cycle (cycles 9-32). 24-hr UPEPs will be performed to confirm and document "CR" response (once serum and random have become negative for monoclonal protein and immunofixation). In patients whose measurable disease is best determined by measuring Bence Jones protein quantification, a 24 hr UPEP will be performed at baseline, day 1 of each cycle 1-8, and day 1 (or within 7 days prior to day 1) of every third cycle during extension phase I and II. Otherwise, 24-hr UPEP Bence-Jones quantification will be estimated from random UPEP specimens performed at baseline, day 1 of each cycle 1-8, and day 1 (or within 7 days prior to day 1) of every third cycle during extension phase[46].
- As of amendment L (version date 05/17/2018), primary endpoint will be MRD (-) CR rate, therefore per the discretion of the investigator, patients without measurable disease may also be enrolled.

6.3.2 Response Criteria adapted from International Myeloma Working Group Criteria for Multiple Myeloma[49] and addition of nCR category[21, 50]

6.3.2.1 Evaluation of Response Criteria

- **MRD(-) CR**
  Complete Response as defined below plus:

  Absence of phenotypically aberrant clonal plasma cells by flow cytometry on bone marrow aspirates using the eight-color two-tube approach developed and validated by LP Flow cytometry lab for MRD detection in multiple myeloma with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.

- **Stringent Complete Response (sCR)**
  Complete Response as defined below plus:

  Normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence (presence/ absence of clonal cells is based on the kappa/ lambda ratio.

- **Complete Response (CR)**
  Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow

- **Near Complete Response (nCR)**
  Defined as absence of myeloma protein on electrophoresis, independent of immunofixation status[50]

- **Very Good Partial Response (VGPR)**

Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24h. If the serum and urine M-protein are unmeasurable, a ≥90% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.

- **Partial Response (PR)**
  ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200mg per 24h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria

- **Stable Disease (SD)**
  Not meeting criteria for CR, VGPR, PR or progressive disease. All 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.

- **Progressive disease (PD)**
  Requires any one or more of the following:

  Increase of ≥25% from lowest response value in the following on 2 consecutive measurements:

  - Serum M-component and/or (the absolute increase must be ≥0.5g/dl). The serum M-component increases of ≥1 gm/dl are sufficient to define relapse if starting M-component is ≥5g/dl.
  - Urine M-component and/or (the absolute increase must be ≥200mg/24h
  - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10mg/dl.
  - Bone marrow plasma cell percentage: the absolute % must be ≥10%
  - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas
  - Development of hypercalcemia that can be attributed solely to the plasma cell proliferative disorder.

- **Relapse from CR**
  Any one or more of the following:

  - Reappearance of serum or urine M-protein by immunofixation or electrophoresis. Appearance of monoclonal or oligoclonal bands that are different from original isotype may not be defined as “relapse from CR”. Oftentimes, such bands may indicate fluctuations in immunological parameters that are not reflective of MM disease. In these situations, immunofixation and electrophoresis will be interpreted by the clinician before being labeled as “relapse”.

  - Development of ≥ 5% plasma cells in the bone marrow

- Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, hypercalcemia.

6.3.3 Progression-Free Survival

PFS is defined as time of start of treatment to time of progression or death, whichever occurs first.

6.3.4 Duration of Best Response

The duration of overall response is measured from the time measurement criteria are met for best response until the first date that recurrent or progressive disease is objectively documented.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. 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#ctc_40).

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet approximately weekly when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

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

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.

- Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Waiver of expedited reporting to CCR

As death and hospitalization due to disease progression are part of the study objectives, and captured as an endpoint in this study, they will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

All events listed below must be reported in the defined timelines to OSROSafety@mail.nih.gov.

The CCR Office of Regulatory Affairs will send all reports to the manufacturers as described below.

Note: All agreements with all manufacturers are no longer active, thus the the below sections are retained only for historical purposes.

8.5.1 SAE Reporting to Amgen

All SAEs, except for TLS, occurring after the subject has signed the informed consent form (ICF) until 30 days after the last dose of any study treatment must be fully documented and reported to Amgen Global Safety as soon as possible but no later than 7 calendar days of initial receipt of the information. **All cases of TLS must be reported to Amgen as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event**

The SAE report forms and the SAE Supplemental Form or MedWatch Form 3500a should be

faxed/emailed together to Amgen Global Safety:

Toll-free U.S. Fax Number: 888-814-8653
For countries where the U.S. toll-free # cannot be used: +44-20-7136-1046
Email (Only for sponsors with a secure email connection with Amgen):
svc-ags-in-us@amgen.com

8.5.2 Reporting Pregnancy to Amgen

8.5.2.1 Contraception/Female

Females of childbearing potential should be advised to avoid becoming pregnant while being treated with carfilzomib. Given that carfilzomib was clastogenic in the in vitro chromosomal aberration test in peripheral blood lymphocytes, as a precaution, females of childbearing potential and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with carfilzomib. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus.

Based on its mechanism of action and findings in animals, carfilzomib can cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in subjects receiving the recommended dose. carfilzomib administered to pregnant rats and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats or up to 0.8 mg/kg/day in rabbits.

If carfilzomib is used during pregnancy, or if the subject becomes pregnant while taking this drug, she should inform the investigator or study staff immediately. The investigator should notify Amgen of the pregnancy and discuss follow-up with the subject. It is not known if carfilzomib will reduce the efficacy of oral contraceptives. Due to an increased risk of venous thrombosis associated with carfilzomib, subjects currently using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception.

The length of time contraception should be used and acceptable contraceptive methods will be discussed with all subjects at the time of enrollment and during participation.

8.5.2.2 Contraception/Male:

Males of reproductive potential should be advised to avoid fathering a child while being treated with carfilzomib. The potential for carfilzomib to be transferred via semen and its effect on sperm are unknown. Male subjects treated with carfilzomib and/ or their female partners (if of childbearing potential) should use effective contraceptive methods or abstain from sexual activity while treated with carfilzomib for 90 days after treatment. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus.

Male subjects should be advised to inform the investigator or study staff immediately in the event that their female partner becomes pregnant during the study. Upon receipt of this information, the investigator should notify Amgen of the pregnancy and discuss follow-up regarding the pregnancy outcome with the subject.

The length of time contraception should be used and acceptable contraceptive methods will be discussed with all subjects at the time of enrollment and during participation.

8.5.2.3 Breast Feeding

No studies of carfilzomib have been conducted in breastfeeding women. Carfilzomib should not be used during breast feeding. Breastfeeding women and women planning on breastfeeding may not participate in clinical trials with carfilzomib. It is not known whether carfilzomib is present in human breast milk. Due to the potential for adverse effects in nursing infants from carfilzomib, a decision should be made whether to discontinue nursing or to discontinue carfilzomib, taking into account the potential benefit of carfilzomib to the mother. If a woman breastfeeds during the study, she must inform the investigator or study staff immediately. The investigator should notify Amgen that the subject has breastfed the infant and discuss follow up with the subject.

8.5.2.4 SAE Reporting to BMS

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to BMS as described below.

Serious adverse events (SAE) are defined above. The investigator must inform BMS in writing using a MedWatch 3500A form of any SAE as soon as possible or at least within 24 hours of being aware of the event. The date of awareness should be noted on the report. The written report must be completed and supplied to BMS by facsimile within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene/BMS tracking number (RV-MM-NCI-0719) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to BMS. A copy of the fax transmission confirmation of the SAE report to **BMS** should be attached to the SAE and retained with the patient records.

Celgene Corporation
Drug Safety
86 Morris Avenue
Summit, N.J. 07901
Toll Free: **(800)-640-7854**
Phone: **(908) 673-9667**
Fax: **(908) 673-9115**
E-mail: mailto:drugsafety@celgene.com

8.5.2.5 Reporting Pregnancy to BMS

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to BMS Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in

reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify BMS Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to BMS Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to lenalidomide should also be reported to BMS Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

If a female partner of a male subject taking lenalidomide becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

BMS Drug Safety Contact Information:

Celgene Corporation
Drug Safety
86 Morris Avenue
Summit, N.J. 07901
Toll Free: **(800)-640-7854**
Phone: **(908) 673-9667**
Fax: **(908) 673-9115**
E-mail: drugsafety@celgene.com

Reporting will be per the collaborative agreement.

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study treatment and for at least 28 days after last dose of lenalidomide and 90 days after the last dose of carfilzomib.

Pregnancy of the patient's partner is not considered to be an AE. the outcome of all pregnancies occurring from the date of the first dose until 28 days after last dose of lenalidomide and 90 days after the last dose of carfilzomib should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,

- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 STATISTICAL CONSIDERATIONS

10.1 SAMPLE SIZE/ACCRUAL RATE

The primary objective of this trial is to determine whether use of CRd is associated with a substantial fraction of patients with high-risk SMM who exhibit at least a VGPR from baseline until the end of 8 cycles of treatment.

The study will initially enroll 12 evaluable patients and determine M-spike levels on each patient pre-treatment as well as after each cycle of treatment. The percent decline from baseline will be determined for each patient. If 12 evaluable patients are enrolled and if 5 or more patients exhibit a VGPR, then the probability of this occurring is 7.3% if the true probability of a VGPR decline is 20%. The probability of 5 or more with a 50% decline is 80.6% if the true probability of a VGPR decline is 50%. Thus, obtaining 5 or more patients out of 12 with a VGPR would provide strong evidence that the true probability of a VGPR was consistent with 50% or more as opposed to 20%.

In order to allow for a small number of inevaluable patients, the initial accrual ceiling will be set at 14.

If 1-2 patients per month can be enrolled on this trial, it expected that accrual could be completed in 6 to 12 months.

Amendment C (version date 07/11/2013) will permit enrollment to a replicate cohort in order to more precisely define the response rate to the CRd regimen in this population. Based on preliminary results from the first 8 evaluable patients on the initial pilot cohort, 7 patients have experienced a VGPR or better response (87.5%). Amendment C (version date 07/11/2013) will allow enrollment of a replicate cohort of 16 evaluable patients in order to estimate the response rate in this cohort independently from the initial cohort of 12 evaluable patients. With 16 evaluable patients, a two-sided 90% confidence interval for the proportion of patients with a VGPR or greater will extend +/- 14% from the observed proportion if the expected proportion is 87%.

Thus, 16 newly enrolled patients will be evaluated for response separately from the initial 12 patients. If the proportions with a VGPR are sufficiently similar (approximately $p>0.35$ by a Fisher's exact test), then in addition to reporting the results separately, an additional result will be the combined proportion of VGPR or greater along with a two-sided 90% confidence interval about this observed proportion. If there are 28 total patients which can be combined in an evaluation, a simple two-sided 90% confidence interval for the proportion of patients with VGPR or greater will extend approximately +/- 11% from the observed proportion if the expected proportion is 86% (24 of 28 responses, for example).

Enrolling additional patients to this replicate cohort will allow the secondary endpoints of duration of response and PFS to be determined with greater precision; it will also allow us to conduct stratified analysis by molecular subtypes (hyperdiploid vs. non-hyperdiploid); and it will provide greater safety data than that available from the pilot cohort of 12 patients.

All 18 patients enrolled on the trial during 2012-2014 exhibited VGPR or better responses, including 17 with some variation of a CR and 16 who were MRD(-). Beginning with Amendment L (version date 05/17/2018), the primary objective of the trial is revised to increase the precision of the estimate of the MRD (-) CR rate. The trial will be extended to enroll a total of 50 evaluable patients to do so. With a total of 50 evaluable patients, the 95% two-sided confidence interval width about a conservative estimate of the MRD (-) CR rate of 70% would be +/- 12.7%. If the MRD (-) CR rate were 85%, 50 patients would permit the estimate to be determined with a 95% two-sided confidence interval of +/- 9.9%.

As of January 2018, a total of 21 patients have been enrolled on the trial and it is anticipated that 1-2 patients per month will continue to be accrued. Thus, it is expected that the remaining 29 patients can be enrolled in approximately 2 years. To allow for a number of inevaluable patients and screen failures, the accrual ceiling will be set at 63.

10.2 STATISTICAL ANALYSIS OF SECONDARY/EXPLORATORY ENDPOINTS

Secondary endpoints are duration of response and progression free survival (both biochemical progression and progression to overt symptomatic multiple myeloma). Duration of response is defined as time from response to disease progression or death. Progression free survival is defined as time of study entry to progression or death. Duration of response and progression free

survival will be estimated using the Kaplan-Meier and log-rank methods. Secondary endpoints will also include rate and duration of MRD-negative CR and OS.

A number of correlative studies will be performed in order to assess carfilzomib in vitro biological activity and investigate minimal residual disease in SMM. Minimal residual disease will be further explored using multi-parametric flow cytometry, PCR-based techniques, and advanced imaging.

Beginning with Amendment L (version date 05/17/2018), the secondary objectives will also include:

1. To estimate the durable MRD (-) CR rate, estimating the fraction of patients who have an MRD (-) CR for 1 year as a minimum. This fraction will be estimated along with a 95% two-sided confidence interval.

2. To compare the outcomes among the 18 patients enrolled in 2014 or earlier to the 32 enrolled in 2017 or later because the diagnostic criteria for SMM vs. MM were revised in 2014 after the 18th patient was enrolled. The MRD (-) CR rates will be compared between these two cohorts of patients using a two-tailed Fisher's exact test. All other comparisons of outcomes between the two cohorts will be interpreted as exploratory and will be done using appropriate non-parametric statistical tests without adjustment for multiple comparisons.

3. To obtain and report safety data on all enrolled evaluable patients to fully characterize the safety of the regimen in a modestly large number of subjects treated on one protocol.

An exploratory objective is also added to evaluate FISH data on available patients enrolled following amendment L (version date 05/17/2018) with respect to classification into high risk vs. non-high-risk patients. Known high risk FISH markers in multiple myeloma literature will be evaluated, namely, 4;14, 14;16, 14;20, del 17p, and 8;14. When available outside lab results will be confirmed either by results from the NCI Laboratory of Pathology or by the Mayo Laboratory results (Test ID: PCPDF, Plasma Cell Proliferative Disorder (PCPD)) and mutual results will be used for the analysis.

11 COLLABORATIVE AGREEMENTS

11.1 AGREEMENT TYPE – CRADA

Note: All agreements with all manufacturers are no longer active, thus the the below text is retained only for historical purposes.

The following CRADAs are associated with this protocol: Amgen, Inc. (formerly directly with Onyx Pharmaceuticals), Inc. for Carfilzomib (#02695); Celgene Corporation for Lenalidomide (#02696).

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

MM is an almost always incurable plasma cell neoplasm that comprises approximately 10%

of all hematologic malignancies, affecting 20,000 patients annually[51]. Recent studies have shown that MM is preceded by MGUS and SMM.[5] Rate of progression at 5 years from high risk SMM to MM is 72-76% at 5 years with a median TTP of < 2 years [12, 13]. MM affects all genders and races. Incidence rates of myeloma is higher among Blacks compared to Caucasians, affecting 14.3 black males per 100, 000 males and 10.0 black females per 100,000 females compared to 6.7 white males per 100, 000 males and 4.1 white females per 100, 000 women. The median age at death for myeloma is 75 years of age[51]. As such, we expect that the majority of patients enrolled in this trial will be older adults of either gender or race. MM patients enrolled on this study will consist of patients referred to and screened at the NIH Clinical Center. There will be no subject selection bias with regard to gender, ethnicity, or race. This protocol excludes lactating and pregnant women from receiving this investigational drug to avoid any possible risks to the fetus or newborn.

12.2 PARTICIPATION OF CHILDREN

Pediatric patients with SMM are extremely rare. Patients under the age of 18 are excluded from this study because inclusion of a rare younger patient will not provide adequate generalizable information to justify their inclusion in this study.

12.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Currently, MM is an incurable malignancy with frequent complications of skeletal fractures, anemia, renal failure and hypercalcemia. Conventional radiographs reveal that 79% of patients will have observed skeletal abnormalities at time of diagnosis[52]. Treatment of high risk SMM patients may reduce skeletal related events from occurring and prevent morbidity from irreversible bone damage seen with MM. In addition, treating SMM with potent anti-MM therapeutics before disease biology becomes aggressive in later disease states may also increase the potential for a cure or prolong progression free survival or overall survival. The added benefit of searching for minimal residual disease markers using FDG-PET CT, flow cytometry, and PCR techniques will allow us to probe depth of response beyond standard insufficient clinical markers.

Risks of the study include exposing asymptomatic patients without clinical MM to chemotherapeutic agents. However, it must be noted that carfilzomib, a new-generation proteasome inhibitor, has been tested in phase 1 trials in combination with lenalidomide and dexamethasone with minimal toxicity and favorable side effect profiles. The most recent phase 1 trial in newly diagnosed MM patients has shown >83% VGPR rates after a median of 8 cycles in 12 patients with <1% neuropathy.[53] Procedures required for obtaining samples/data for experimental purposes (venipuncture, urine collection, PET/CT scan, DW-MRI and bone marrow biopsy) are of limited risk to the patient. Although patients will suffer some additional pain or discomfort from the PET/CT scans and annual bone marrow biopsies, clinical experience has shown that the medical risk is limited.

The genetic testing performed on the study carries with it a potential loss of privacy in case of database compromise, as well as psychological distress to participant and possibly family members in the event that incidental findings are disclosed.

12.3.1 Known Potential Risks

12.3.1.1 Radiation Exposure

On this study, patients will receive approximately three FDG PET/CT scans (as indicated in section **5.1.3.1**). The procedures for performing FDG PET/CT scans will follow clinical policies, no special procedures apply to these assessments for research purposes.

The total radiation dose for research purposes will be approximately 3.6 rem.

12.3.1.2 Blood draws

Pain and bruising in the area where the blood was drawn, lightheadedness, fainting due to transient lowering of blood pressure, and infection at the blood-drawing site.

12.3.1.3 Questionnaires

Emotional discomfort associated with answering potentially uncomfortable questions.

12.3.1.4 Intravenous Catheter

Pain, bleeding, infection, and collapsed lung. The long-term risks of the catheter include infection and clotting of veins.

12.3.1.5 Bone marrow aspiration and biopsy

Local bleeding, pain at the site, infection, allergy to the local anesthetic, and soreness at site.

12.3.1.6 PET/CT and DW-MRI scans

PET/CT may cause physical discomfort during the placement of an intravenous line and the necessity to remain still on back for 30 minutes. The DW-MRI may cause physical discomfort due to necessity to remain still on back for about 1½ hours.

12.3.1.7 Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

Learning of genetic risks for another disease or disability may cause emotional distress.

12.4 Risks/Benefits Analysis

Given the high rates of progression specific to the high risk SMM populations and low toxicity profile of combination therapy, risk of exposure does not seem to outweigh the clinical benefit that patients may derive from therapy. More importantly, much of patient morbidity in MM is associated with pain from irreversible skeletal related events. Such a trial would aim to treat or cure the disease before irreversible bone damage occurs or before aggressive clinical MM occurs. Discomfort from venipuncture, bone marrow biopsy, PET/CT scan and DW-MRI is minimal and of limited risk compared to the knowledge gained by depth of response from disease monitoring.

12.5 Consent Process and Documentation

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Consent for the optional biopsies performed on this study will be obtained at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures.

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location, but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

NOTE: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at:
https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

12.5.1 Request for Waiver of Consent of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in section **2.2.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the

design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by the NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH Clinical Center.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

14.1 CARFILZOMIB (IND # 112587)

14.1.1 Source

Carfilzomib is provided to investigator by Amgen, Inc.

14.1.2 Toxicity

A comprehensive listing of all toxicities (i.e., very common, common, etc.) are listed in the informed consent document. The approved USPI may also be referenced for current information related to this agent. See below information regarding most significant toxicities:

Fetal Risk
Do not use Carfilzomib during pregnancy. If Carfilzomib is used during pregnancy, it may cause birth defects or death to a developing baby. Women of childbearing potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after Carflizomib treatment.

Tumor Lysis Syndrome:
Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Most common adverse reactions:
Fatigue, vomiting/nausea, fever, respiratory infection, hypertension, diarrhea, loss or decrease of appetite, insomnia, neutropenia, peripheral edema

Very rare and serious adverse reactions:

Cytomegalovirus, progressive multifocal leukoencephalopathy (PLM), pericarditis, pancreatitis, posterior reversible encephalopathy syndrome (PRES), cholestasis, hepatitis B virus reactivation, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)

14.1.3 Formulation and preparation

14.1.3.1 Formulation

Carfilzomib for injection is a sterile, white to off-white lyophilized powder and is available as a single-use 60 mg vial. Each 60 mg vial contains 60 mg of carfilzomib, 3000 mg sulfobutylether beta-cyclodextrin, 57.7 mg citric acid, and sodium hydroxide for pH adjustment (target pH 3.5).

14.1.3.2 Preparation

Vials will be reconstituted with Sterile Water for Injection to a concentration of 2 mg/mL by adding 29 mL to the 60 mg vial. The calculated dose will be withdrawn from the vial and further diluted into a 100 mL intravenous bag of 5% Dextrose Injection, USP. Refer to the FDA-approved labeling for detailed reconstitution and dilution instructions.

14.1.3.3 Inspection

The reconstituted drug solution in the vial should be a clear liquid. Inspect all vials for the presence of any suspended particles, particulate matter, discoloration or hazy solution prior to administration.

If the solution is not clear or particles exist in inspected vials, record the observation in the appropriate Drug Accountability Log and notify Amgen immediately.

- DO NOT USE THE DRUG.
- Place the vial(s) into a plastic bag labeled as "Quarantined" with the date.

- Store labeled quarantined drug in a temperature-monitored refrigerator and ensure they are physically segregated from the drug that is available for use.
- Amgen will instruct the clinical site on how to proceed with quarantined vial(s).

14.1.3.4 Calculation of Dose

Each dose will consist of Carfilzomib for Injection administered on a mg/m^2 basis and should be based on the patient's actual calculated body surface area (BSA).

The BSA should be calculated based upon the institution's practice and method of calculation should remain consistent throughout a subject's participation in the trial.

Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA.

14.1.4 Stability and Storage

14.1.4.1 Lyophilized Drug Product

Lyophilized Carfilzomib for Injection must be kept in the labeled drug cartons and stored at 2°C - 8°C (36°F - 46°F) in a refrigerator.

If procedures permit, the refrigerator should be continuously monitored, and temperature records retained for review.

The refrigerator should also be on a backup generator and alarmed for temperature deviations if available. Lyophilized Carfilzomib for Injection exposed at any time to temperatures exceeding 30°C / 86°F must be discarded

14.1.4.2 Reconstituted Drug Product

Once a drug vial is reconstituted and inspected, the clear solution can be stored in a refrigerator (recommended) controlled from 2°C - 8°C (36°F - 46°F) or at room temperature from 15°C - 30°C (59°F - 86°F) until use. Once reconstituted, Carfilzomib for Injection is stable for a total of 24 hours. DO NOT FREEZE LYOPHILIZED OR RECONSTITUTED DRUG.

14.1.4.3 Diluted Drug Product

After dilution with 5% Dextrose Injection for clinical use, Carfilzomib should preferably be stored under refrigeration unless plan for administration immediately following preparation. Diluted Carfilzomib is stable for 24 hours in the refrigerator or 4 hours at room temperature from the time of vial reconstitution. If refrigerated, the infusion solution should be equilibrated to room temperature prior to administration.

14.1.5 Administration procedures

Carfilzomib will be administered by intravenous infusion over 30 minutes through a peripheral or central venous access device as a secondary infusion into a primary line containing 5% Dextrose Injection. Infusions can be stopped or slowed down if patient is experiencing infusion reactions.

Do not mix carfilzomib with or administer as an infusion simultaneously with other drugs.

Flush line AFTER drug administration with a minimum of 50 mL of 0.9% Normal Saline or 5% Dextrose Injection (particularly for infusions through a peripheral line to minimize phlebitis risk).

14.1.6 Incompatibilities

In an in vitro study using human liver microsomes, carfilzomib showed modest direct and time-dependent inhibitory effect on human cytochrome CYP3A4/5. Given that the clearance of carfilzomib likely occurs extrahepatically via the activity of epoxide hydrolase and peptidase activities, the clinical relevance of these in vitro results is not clear. No clinically significant drug interactions have been noted to date in patients receiving a variety of agents metabolized by CYP3A4. Moreover, no dose adjustments have been required for any concomitant medication in patients receiving carfilzomib. However, caution should be exercised in administration of concomitant medications which are substrates of human CYP3A4.

14.2 LENALIDOMIDE

14.2.1 Source

REVLIMID® (lenalidomide) is provided to investigator by Celgene Inc. under Cooperative Research and Development Agreement (CRADA).

14.2.2 Toxicity

A comprehensive listing of all toxicities (i.e., very common, common, etc.) are listed in the informed consent document. The approved USPI may also be referenced for current information related to this agent. See below information regarding most significant toxicities:

Fetal Risk
Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing baby. In women of childbearing potential, obtain 2 negative pregnancy tests before starting REVLIMID® treatment. Women of childbearing potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment.

Hematologic Toxicity
REVLIMID can cause significant neutropenia and thrombocytopenia. In the pooled MM studies Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of REVLIMID and dexamethasone than in patients treated with dexamethasone alone.

Deep Vein Thrombosis and Pulmonary Embolism
Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with MM treated with lenalidomide combination therapy. A significantly increased risk of DVT and PE was observed in patients with MM who were treated with REVLIMID and dexamethasone therapy in a clinical trial.

Allergic Reactions
Angioedema, anaphylaxis, and serious dermatologic reactions including Stevens-Johnson syndrome

(SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not

receive REVLIMID. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions.

Tumor Lysis Syndrome
Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Most common adverse reactions (≥20%)
Fatigue, neutropenia, constipation, diarrhea, muscle cramp, anemia, pyrexia, peripheral edema, nausea, back pain, upper respiratory tract infection, dyspnea, dizziness, thrombocytopenia, tremor and rash.

Rare and Serious adverse reactions

Myocardial infarction, myocardial ischemia, cardiac failure, gastrointestinal hemorrhage, intestinal obstruction; meningitis, infections of the skin, joints, and kidney; abnormal levels of blood sugars and electrolytes, hypoxia, hepatocellular injury.

14.2.3 Formulation and preparation

Lenalidomide will be supplied as capsules for oral administration. Bristol Myers Squibb (BMS) will provide lenalidomide 5, 10, 15 and 25 mg capsules for the Induction Phase of the protocol and for the extended dosing phase(s).

14.2.4 Stability and Storage

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

14.2.5 Administration procedures

Bristol Myers Squibb (BMS) will supply Revlimid® (lenalidomide) to the Clinical Center Pharmacy to be dispensed to study participants at no charge through the REMS® program. Lenalidomide will be shipped directly to patients or picked up directly from the Clinical Center pharmacy. Bottles will contain a sufficient number of capsules for one cycle of dosing; no more than a one-month supply of lenalidomide may be dispensed at one time.

11.2.6 Incompatibilities

Results from human in vitro metabolism studies and nonclinical studies show that REVLIMID is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450- based metabolic drug interactions in man.

Digoxin
When digoxin was co-administered with lenalidomide, the digoxin AUC was not significantly

different; however, the digoxin Cmax was increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of lenalidomide.

Warfarin
Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of single 25-mg dose warfarin had no effect on the pharmacokinetics of total lenalidomide. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide administration.

Concomitant Therapies That May Increase the Risk of Thrombosis
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in MM patients receiving lenalidomide with dexamethasone.

14.3 DEXAMETHASONE

14.3.1 Source

Dexamethasone will be provided from commercial sources by the NIH Clinical Center Pharmacy Department.

14.3.2 Toxicity

Common

Cardiovascular: Hypertension

Dermatologic: Atrophic condition of skin, Finding of skin healing, Impaired

Endocrine metabolic: Cushing's syndrome, Decreased body growth

Gastrointestinal: Disorders of gastrointestinal tract

Immunologic: At risk for infection

Musculoskeletal: Osteoporosis

Ophthalmic: Cataract (5%), Raised intraocular pressure (25%)

Psychiatric: Depression, Euphoria

Respiratory: Pulmonary tuberculosis

Serious

Endocrine metabolic: Hyperglycemia, Primary adrenocortical insufficiency

Ophthalmic: Conjunctival hemorrhage (22%), Glaucoma, Vitreous detachment (2%)

14.3.3 Formulation and preparation

Oral Tablet (Scored): 4 mg

Injection, solution, as sodium phosphate: 4 mg/mL (1 mL, 5 mL, 30 mL)

14.3.4 Administration procedures

Oral: Administer with meals to decrease GI upset.

I.V.: Administer intravenously over 10 minutes.

14.3.5 Incompatibilities

Contraindicated: Praziquantel (theoretical), Rotavirus Vaccine, Live (established)

Major: Aldesleukin (theoretical), Bupropion (theoretical), Darunavir (theoretical), Dasatinib (theoretical), Etravirine (theoretical), Fosamprenavir (theoretical), Imatinib (theoretical), Ixabepilone (theoretical), Lapatinib (theoretical), Nilotinib (theoretical), Quetiapine (probable), Romidepsin (theoretical), Sunitinib (theoretical), Temsirolimus (theoretical), Thalidomide (probable).

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16 APPENDICES

APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: REQUIREMENTS FOR REMS

Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Requirements for REMS

- Patients should be instructed never to give lenalidomide to another person.
- Patients will be asked to take part in a mandatory confidential survey prior to initiation of lenalidomide. To take the survey, they will be instructed to call the BMS Customer Care Center at 1-888-423-5436. Male patients will be asked to take the survey monthly. Female patients will be asked to take survey periodically (monthly if females of childbearing potential and every 6 months if females of not childbearing potential).
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- All patients will be required to sign the REVLIMID, Patient-Physician Agreement Form.
- Males must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy. See below for further details
- Females of childbearing potential must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation. See below for further details.

Females not of childbearing potential must sign the REVLIMID, Patient-Physician Agreement Form that says you are presently not pregnant and do not have the ability to have children.

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory REMS® program, and be willing and able to comply with the requirements of REMS®.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female 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).

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

Female Patients: FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients: Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

APPENDIX C: BONE MARROW ASPIRATE COLLECTION, SORTING AND STORAGE

Collection of Bone Marrow

NOTE: Refer to Section **5.1** for correlative study bone marrow time points and Study Calendar (Section **3.4**).

- Orders for bone marrow biopsies should be placed in the Clinical Research Information System (Clinical Research Center, NIH, Bethesda, MD).
- Notify the CCR Hematology lab that flow immunophenotyping is being performed (301-496-4473). The hematology BM collection tech will bring a 10 mL tube sodium heparin Vacutainer tube to the specimen collection site and prepare an extra smear for the Flow Cytometry Laboratory.
- Get sterile heparin suitable for injection from the nurse's station. Rinse syringe and needle with sterile heparin, leaving no less than 0.5 mL in syringe.
- Bone marrow samples will be collected as bone marrow core biopsies and aspirates for analyses. Aspirate first 2 cc of marrow for morphology first and give specimen to Hematology lab technician to be given to Hematology Section, Department of Lab Medicine (1 mL will go to Hematopathology and 1 mL (optionally) will be delivered to Irina Maric, MD for research assessing proteasomes). Reposition needle and, for cellular specimens, aspirate 5-8 mL of bone marrow for flow cytometry and cell sorting in heparin containing syringe.
- Bone marrow core biopsies and one fraction of marrow aspirates will be fixed and paraffin-embedded for histological/immunohistochemical analysis and long term storage. One fraction of marrow aspirates will be stored as air-dried aspirate smears and the rest will be frozen.
- After processing in the pathology department, clot sections will be sent to the Molecular Diagnostics Core Laboratory, LP, NCI under the direction of Mark Raffeld, MD for determination immunoglobulin heavy and/or light chain rearrangement, and KRAS/NRAS mutations (No longer being done, as of Amendment H (version date 06/12/2017).
- For aspirate specified for flow cytometry under the direction of Hao-Wei Wang, immediately discharge 1 mL of aspirated marrow syringe into a 10mL sodium heparin Vacutainer, cap tube tightly and mix by gentle inversion 5-6 times. Label tube with patient name, unique identifier number and date. Deliver immediately to the Flow Cytometry Laboratory 3S240 (specimens containing hematopoietic neoplasms have a tendency to clot and must be processed immediately). Call for STAT Escort pickup and delivery if you cannot deliver the specimen yourself (301-496-9295). Aspirate from marrows at baseline, end of cycle 8/or CR reached between cycles 1-8, end of cycle 20/or CR reached between cycles 9-20 and during treatment termination/or CR reached between cycles 21 and beyond will be sent for plasma cell flow cytometry immunophenotyping at Hao-Wei Wang's lab.
- For aspirate designated for CD138 sorting, VDJ sequencing, exome sequencing, and microenvironment studies, send remaining aspirate sample to the Young Laboratory (Building 10/4N106) Place aspirate sample in EDTA syringe immediately on ice. Transfer within 30 minutes of sampling to the lab for processing. For baseline samples, cells will be sorted in CD138+ and – fractions. CD138+ plasma cells will be viably frozen and batched to be sent to Adaptive Technologies for VDJ sequencing and to

MSKCC for exome sequencing. CD138- fractions will be studied by Dr.'s Wang and Young. At subsequent time points, CD138+ sorting will not be done if the patient is in remission. **Note:** As of February 6, 2023, all participants have completed the maintainance phase (C32) thus bone marrow and peripheral blood research samples will be sent to Ryan Young's lab on a case to case basis.

- For aspirate specified for cytogenetics/FISH, aspirate, as of amendment H (version date 06/12/2017), FISH/cytogenetic information may be derived from the patient's outside records or performed on baseline bone marrow samples at a third-party testing laboratory per the CC DLM clinical laboratory protocol/procedure which currently is the Mayo Laboratory Test ID: PCPDF, Plasma Cell Proliferative Disorder (PCPD).
- For aspirate specified assessing proteasomes: 1 mL will be delivered to Irina Maric, MD for research assessing proteasomes. After Amendment H (version date 06/12/2017), this is optional.

APPENDIX D: PERIPHERAL BLOOD AND URINE COLLECTION AND STORAGE

Blood Processing Core

Refer to Sections **3.4** (Study Calendar) and **5.1** for research blood and urine collection time points.

Venipuncture

- Up to 100 mL of peripheral blood will be collected into serum separator tubes (SST), sodium heparin tubes (GTT) or EDTA tubes. The amount of blood collected will be dictated by the number of experiments to be performed, and by the patient's peripheral blood count.
- Serum
  - Collect 7-10 mL blood in a serum separator tube (SST).
  - Allow the blood to clot by standing at room temperature for 30 minutes.
  - Separate serum from cells by centrifuging at 4 degrees C for 5 minutes at 1200xg.
  - Pipette 2 aliquots of 1.5mLs each into two 2mL cryovials.
  - Freeze immediately at -20 or lower
  - Maintain in -80 freezer for storage until shipment
- Plasma
  - Collect 7 mL blood in a sodium heparin tube (green top).
  - Place immediately on wet ice and refrigerate until time of processing.
  - Separate plasma from cells by centrifuging at 4 degrees C for 5 minutes at 1200xg.
  - Pipette 2 aliquots of 1.5mLs each into two 2mL cryovials.
  - Freeze and store in -80C freezer.
- Complete blood count
  - A venous blood sample for a CBC will be collected in a 10ml EDTA lavender top (BD EDTA 366643) tube. Keep at room temperature until processing begins.

Urine Sample Collection

- Approximately 45 mL of urine will be collected into a standard urine collection cup for further analysis. The amount of urine collected will be dictated by the number of experiments to be performed.
- Transfer to a screw-cap conical tube
- Freeze immediately at -20 or lower
- Maintain in -80 freezer for storage until shipment

Labeling of Samples

All specimens are to be labeled per the local site's standard procedures. The following information, if not provided on the specimen label, must be linked to the specimen label and provided on the inventory sheet:

- patient study ID #

  - sample type
  - date/time of draw (DD/MMM/YY 24:00)
  - time point (ex. C1D1 pre, C1D1 24hr post)
  - any collection issues (short draw, delayed processing, etc.)
  - protocol title/number
  - institute name
  - contact information
- Do not include the patient name, medical record number, or initials.