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

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Investigational Agents:

Drug Name:	Carfilzomib
IND Number:	112587
Sponsor:	Ola Landgren MD, PhD
Manufacturer:	Onyx Pharmaceuticals, Inc.

Commercial Agents: Dexamethasone, Lenalidomide

Celgene's 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.[1-2]
- 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". [3]
- Carfilzomib is a new proteasome inhibitor with potent anti-MM effects

Objectives:

Primary Endpoints:

- The primary objective of the study is to assess the response rate of CRd in patients with high-risk SMM.[4]

Secondary Endpoints:

- To determine progression free survival (PFS)
- To determine duration of response (DOR)
- To evaluate toxicity of combination therapy (carfilzomib, lenalidomide, and dexamethasone).
- To evaluate biological activity of carfilzomib and correlate to clinical outcomes (gene expression profiling (GEP) on pre and post carfilzomib exposure bone marrow samples)

Eligibility:

- SMM according to the International Myeloma Working Group definition [3] i.e.:
  - Serum M-protein ≥3 g/dl and/or bone marrow plasma cells ≥10 %,
  - 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
- 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)
- "High-risk SMM" per Mayo Clinic[2] or Spanish PETHEMA[1] criteria
- Age ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Male or female patient who accepts and is able to use recognised effective contraception (oral contraceptives, IUCD, barrier method of contraception in conjunction with spermicidal jelly) throughout the study when relevant
- Absolute neutrophil count (ANC) ≥1.0 K/uL, hemoglobin ≥8 g/dL, and platelet count ≥ 75 K/uL

- Adequate hepatic function, with bilirubin < 1.5 x the ULN, and AST and ALT < 2.5 x ULN
- Calculated creatinine clearance ≥ 60 mL/min as determined by the Cockcroft-Gault formula: CrCl = (140 – Age) x Mass (in kilograms) x [0.85 if Female] 72 x Serum Creatinine (in mg/dL). If calculated CrCl based on Cockcroft-Gault method is <60 mL/min, patient will have a 24 hr urine collection to measure CrCl. The measured CrCl must also be ≥ 60 ml/min.

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 will undergo stem cell collection
- After 8 cycles of CRd, Patients will receive lenalidomide maintenance for 12 cycles
- Patients will have routine blood work with SPEP and free light chains monthly
- Pre- and post-treatment bone marrow biopsies will be obtained for confirmation of diagnosis 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 enrolling 12 evaluable patients to detect a VGPR from baseline

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

- The primary objective of the study is to assess the response rate of CRd in patients with high-risk SMM.[4]

1.1.2 Secondary Objective(s):

- To determine progression free survival (PFS)
- To determine duration of response (DOR)
- 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)

1.2 BACKGROUND AND RATIONALE:

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.[5] 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.[6-8] 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.[9-10] 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.[11] 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.[12-13] 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).[14] 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.[15] SMM can be risk stratified into categories using Mayo Clinic[2] risk criteria and Spanish PETHEMA[1] risk criteria. 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 of progression to active disease and overall survival [16]. 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 [17]. In May 2011, an intention to treat (ITT), interim analysis (n=58) presented at the International Myeloma Workshop in Paris [18] 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 ($p<0.05$).

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 [19]. 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 overaccumulation 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 [20-21]. 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 [22].

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 [23]. In the aforementioned phase I/II study, with combination bortezomib, lenalidomide, and dexamethasone, 80% of treated patients experienced sensory neuropathy all grades [22]. 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 [24].

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 [25-27]. In vitro models suggest carfilzomib has activity against bortezomib resistant myeloma cell lines [26]. Carfilzomib can also work synergistically with dexamethasone to enhance tumor cell death [26]. 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.

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 lenalidomide maintenance treatment (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, and detection of clonality using heavy and/or light chain immunoglobulin rearrangement.

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 Laboratory of Pathology, NCI based on the International Myeloma Working Group Criteria[3]:

- Serum M-protein ≥3 g/dl and/or bone marrow plasma cells ≥10 %
- 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

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)

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 ≥1.0 K/uL
- 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) ≤2.5 X institutional upper limit of normal
- Creatinine Clearance ≥ 60 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). If calculated CrCl based on Cockcroft-Gault method is <60 mL/min, patient will have a 24 hr urine collection to measure CrCl. The measured CrCl must also be ≥ 60 ml/min.

2.1.1.6 "High-risk SMM" per Mayo Clinic[2] or Spanish PETHEMA[1] criteria

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

2.1.1.8 The effects of carfilzomib and lenalidomide on the developing human fetus are unknown. For this reason and because immunomodulatory agents as well as other therapeutic agents used in this trial 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 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: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods. 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.

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

[†] 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).

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

- Treatment with corticosteroids for other indications is permitted
- Patients with prior proteasome inhibitor therapy will be excluded

2.1.2.3 Patients with a diagnosis of MM

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.

2.1.2.6 Uncontrolled hypertension or diabetes

2.1.2.7 Pregnant or lactating females. Pregnant women are excluded from this study because Carfilzomib/Lenalidomide are agents with the potential for teratogenic or abortifacient effects. 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. These potential risks may also apply to other agents used in this study

2.1.2.8 Significant cardiovascular disease with NYHA Class 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 5years

2.1.2.14 Major surgery within 1 month prior to enrollment

2.1.3 Recruitment Strategies

2.1.3.1 Patients from the SMM and MGUS Natural History Study (NCI Protocol: 10-C-0096) will be potential candidates.

2.1.3.2 Other participant sources will be from outside physician referrals.

2.1.3.3 Our ongoing natural history study and outside physician referral network has a high representation of minorities

2.2 SCREENING EVALUATION

2.2.1 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.

2.2.2 The following studies and laboratory tests will be completed 4 weeks prior to study entry:

2.2.2.1 CBC with differential and reticulocyte count

2.2.2.2 Acute Care, Mineral and Hepatic Panels, and CrCl calculation

2.2.2.3 Uric acid, LDH, and Beta-2 Microglobulin

2.2.2.4 PT, PTT

2.2.2.5 Serum protein electrophoresis (SPEP) and immunofixation to assess for presence and quantity of monoclonal protein (M-protein)

2.2.2.6 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.

2.2.2.7 Serum free light-chain studies, determined using the FreeliteTM assay system

2.2.2.8 Quantitative immunoglobulins

2.2.2.9 Viral serologies: Hepatitis B surface antigen Anti Hepatitis C (HCV) antibody. If positive, will follow with HCV RNA PCR

2.2.2.10 If the patient does not meet Mayo Clinic criteria 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 Section 2.4.1.1) to minimize the number of bone marrow biopsies

2.2.2.11 Serum or urine pregnancy test in women of child-bearing potential.

2.2.2.12 12-lead EKG

2.2.2.13 A skeletal survey of the axial and appendicular skeleton will be performed. Exception may be made if skeletal survey has been performed within the past 3 months and was found to be positive.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://intranet.cancer.gov/ccr/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4 BASELINE EVALUATION

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

2.4.1.1 Bone Marrow (see Section 5)

1. Histopathological evaluation on bone marrow aspirate and biopsy
2. Immunophenotyping of aberrant clonal plasma cells by multiparametric flow cytometry.
3. Interphase FISH/cytogenetics
4. CD 138+ fractions and CD 138- fractions cell sorting with subsequent correlatives on both fractions.
5. Proteasome activity and quantification (peripheral blood and bone marrow).
6. Immunoglobulin heavy and/or light chain rearrangement.

2.4.1.2 Peripheral Blood/Urine

1. Peripheral blood and urine samples for storage and establishing a biobank. Appendix D
2. Subunit profiling and activity of circulating proteasomes by enzyme-like immunosorbent assay.
3. Apoptosis assays to identify necrotic or late stage apoptotic cells.
4. Immunolocalization studies.
5. Peripheral blood flow cytometry assessing for circulating plasma cells under the direction of Maryalice Stetler-Stevenson, MD
6. 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.

2.4.2 FDG PET/CT scan within 4 weeks of study entry and prior to starting therapy.

2.4.2.1 Prior to ^{18}F-FDG PET/CT imaging, the subject will be fasted and have 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 fingerstick. 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 Molecular Imaging Clinic (MIC) on the day of their 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 1-hour, and again at 2-hours post injection. PET/CT standard operating procedures. The patient will be instructed to maintain good hydration in order to reduce the radiation dose. The radiation dose from the procedure will be a maximum of 4.1 rem per year; this is within the RSC guidelines of 5.0 rem per year for adults.

3 STUDY IMPLEMENTATION

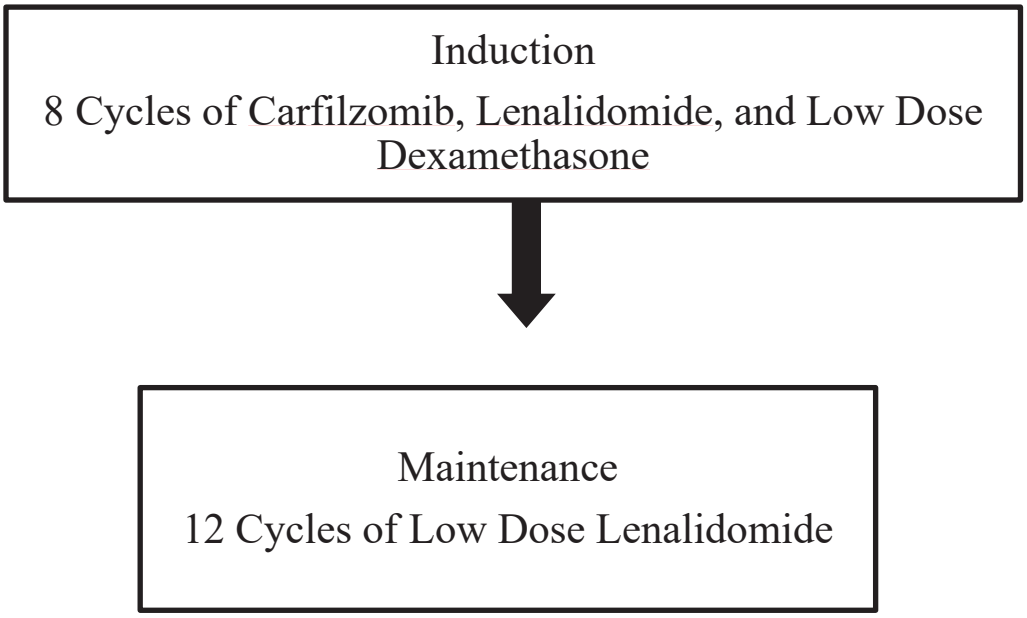
3.1 STUDY DESIGN

3.1.1 12 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 maintenance lenalidomide for 12 cycles.

- 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 (exception: lenalidomide is NOT given on cycle 1, day 1)
- Cycles 1-4: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15, 16, 22, and 23 (exception: dexamethasone is NOT given on cycle 1, day 1)
- Cycles 5-8: Dexamethasone 10 mg/dose, days 1, 2, 8, 9, 15, 16, 22, and 23, followed by:
- Maintenance lenalidomide for 12 cycles.

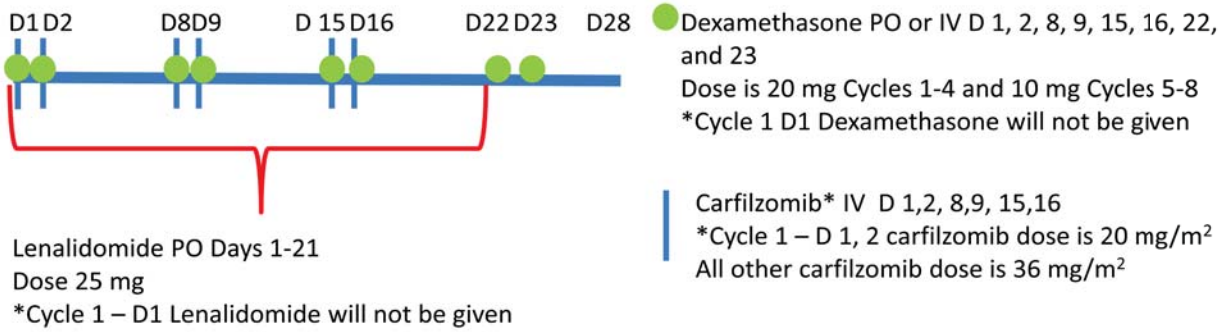
3.1.2 After receiving first 4 cycles, patients who are considered to be eligible for subsequent high dose therapy/autologous stem cell transplant (ASCT) will be encouraged to undergo autologous stem cell harvesting for potential use in the future. Collection and delivery can be conducted at outside institutions. 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. Harvesting and delivery of high dose therapy/autologous stem cell transplant, conducted at NIH Clinical Center will not be included in this current protocol.

3.1.3 After 8 cycles, patients will proceed to extended dosing phase of lenalidomide (Days 1-21 of 28 day cycle) for 12 cycles.



3.2 DRUG ADMINISTRATION

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



- Agents:
  a) Carfilzomib:
     i) 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
     ii) Cycle 2-8: 36mg/ m^2 IV infusion over 30 minutes on days 1, 2, 8, 9, 15, and 16
  b) Lenalidomide:
     i) Cycle 1: 25 mg oral days 2-21 of 28-day cycle
     ii) Cycle 2 - 8: 25 mg oral days 1-21 of 28-day cycle
  c) Dexamethasone:
     i) Cycle 1: 20 mg oral or IV on days 2, 8, 9, 15, 16, 22, and 23
     ii) Cycle 2-4: 20 mg oral or IV on days 1, 2, 8, 9, 15, 16, 22, and 23
     iii) Cycle 5-8: 10 mg oral or IV on days 1, 2, 8, 9, 15, 16, 22, and 23
- In Cycle 1, the following adjustments to the dosing schema will be implemented:
  a) Cycle 1 Day 1, carfilzomib will be administered alone.
  b) Patients will be admitted and observed as an inpatient while receiving Cycle 1 Day 1 and 2 therapy.
  c) Carfilzomib will be given at a lower dose of 20 mg/m^2 on Days 1 and 2 of Cycle 1.
  d) Lenalidomide and Dexamethasone will not be given on day 1
  e) Bone marrow biopsy with aspiration will be performed at baseline and Cycle 1 Day 2
  f) Hydration will be administered prior and subsequent to carfilzomib dosing.
     i) 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.

ii) 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 D1 and D2. 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
- Patients will be required to take oral Aspirin 81 mg or 325 mg or alternative anticoagulation therapy every day for the duration of their participation in the study).
- Patients will be required to take oral acyclovir 800 mg BID or oral valacyclovir 500 mg daily for viral prophylaxis throughout all cycles in which carfilzomib is given.
- 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. Lenalidomide will be provided in accordance with the RevAssist® program of Celgene Corporation. Per standard RevAssist® 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 RevAssist® program. Prescriptions must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**
- Harvesting Stem Cells:

1) 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.

2) 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.

3) 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.

4) Transplant eligible patients will be defined as age <75 years with no significant disease co-morbidities and ECOG ≤2.

- Extended Dosing Phase: Cycles 9-20:

1) Patients will go on to receive additional maintenance phase therapy with oral lenalidomide 10 mg/dose, given daily for 21 days of a 28 day cycle, for 12 cycles.

2) Lenalidomide ordered in the extended dosing phase of the study can be prescribed by local treating physicians or NIH clinical center physicians.

3) Patients will be required to take oral Aspirin 81 or 325 mg or alternative anticoagulation therapy every day for the duration of their participation in the study

3.3 DOSE MODIFICATIONS

3.3.1 Dose Reductions

	Lenalidomide	Carfilzomib
Baseline dose	25 mg daily on Days 1-21 of 28 day cycle	36 mg/m^2
One level dose reduction	20 mg daily on Days 1-21 of 28 day cycle	27 mg/m^2
Two level dose reduction	15 mg daily on Days 1-21 of 28 day cycle	20 mg/m^2
Three level dose reduction	10 mg daily on Days 1-21 of 28 day cycle	
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 Initiation of new cycle will start on the scheduled Day 1 of a new cycle if:

- ANC ≥ 1.0 K/uL
- Platelet count ≥ 75 K/uL

- 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 or the conditions listed above are met. 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

3.3.3 Hematologic Toxicity

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.

3.3.4 Non-Hematologic Toxicity

3.3.4.1 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.

3.3.4.2 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.

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

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

Common 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 formula: CrCl = (140 – Age) x Mass (in kilograms) x [0.85 if Female] 72 x Serum Creatinine (in mg/dL)	• CrCl 31-60 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.

Common 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.

3.3.5 Monitoring

3.3.5.1 Patients will be observed in the hospital for administration of cycle 1 Days 1 and 2 of therapy.

3.3.5.2 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 thereafter.

3.3.5.3 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. Subsequent serum immunofixation will only be performed on those patients clinically indicated

3.3.5.4 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, during cycles 1-8 if patient obtains CR or at the end of cycle 8 if no CR is achieved, and during cycles 9-20 if patient obtains CR or at the end of cycle 20 if no CR is achieved.

3.3.5.5 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 of each cycle thereafter.

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

3.3.5.7 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 is achieved, and during cycles 9-20 if patient obtains CR or at the end of cycle 20 if no CR is achieved. At PI discretion, patient may be asked to have an additional PET-CT at progression. The radiation dose from the procedure will be a maximum of 4.1 rem per year; this is within the RSC guidelines of 5.0 rem per year for adults.

3.4 STUDY CALENDAR

Study	Pre-treatment	Induction Treatment							Maintenance Treatment			Follow-Up	Disease Progression at any Time Point[k, o]
		Cycle 1					Cycle 2-8		Cycles 9-20			Every 3-6 months[j, o]	
		Day 1	Day 2	Day 8	Day 15	Day 22	Day 1[o]	CR Achieved/End of Cycle 8[l, m, n, o]	Day 1[o]	Day 1 12, 15, 18[o]	CR Achieved/End of Cycle 20[l, m, n, o]		
Medical Record Review	x											x	
H&P	x	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			x	
Urine for UPEP and IFE [l]	x							x			x		
Viral Studies[b]	x												
Register for RevAssist	x												
Pregnancy Test[c]	x[c]	x[d]	x[d]	x[e]	x[e]	x[e]	x[c]		x[c]				
Myeloma tests[f]	x						x		x			x	
Research Blood/Urine	x		x	x	x		x	x		x	x		x
Bone Marrow/Aspirate	x[g]		x[h]					x[i, n]			x[i, n]		x
Skeletal Survey	x												
FDG PET-CT	x							x[m]			x[m]		x
Adverse Events/Toxicity		x	→	→	→	→	→	→	→	→	→	→	
12 lead EKG	x												

a. Routine tests include CBC with differential, reticulocyte count, Acute Care, Mineral and Hepatic Panels, uric acid, eGFR determination and LDH. 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)

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

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 and heavy/light chain immunoglobulin rearrangement and/or NRAS/KRAS mutations in Molecular Pathology

h. Cycle 1 Day 2 bone marrow require aspirate alone sent for CD138 sorting (GEP studies and microenvironment studies), flow cytometry for proteasomes and (optional) autophagy markers.

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, DLM, flow cytometry (bone marrow immunophenotyping of plasma cells, and +/- optional assessment of proteasomes), CD 138 sorting/GEP/storage, and +/- heavy/light chain immunoglobulin rearrangement and/or NRAS/KRAS mutations in Molecular Pathology (optional)

j. At minimum, follow-up will be every 3-6 months until progression of disease, institution of alternative therapy, or death. Patients may be followed at more frequent time intervals if clinically indicated, ie 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.

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 baseline, during cycles 1-8 if patient achieves CR or at the end of cycle 8 if no CR is achieved, and during cycles 9-20 if patient achieves CR or at the end of cycle 20 if no CR is achieved.

m. FDG-PET scan will be performed on patients in the Molecular Imaging Department at baseline, during cycles 1-8 if patient achieves CR or at the end of cycle 8 if no CR is achieved and during cycles 9-20 if patient achieves CR or at the end of cycle 20 if no CR is achieved. FDG-PET scan can be performed +/- 21 days of intended cycle day.

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, and during cycles 9-20 if patient achieves CR or at the end of cycle 20 if no CR is achieved. Bone marrow aspirate and biopsy can be performed +/- 21 days of intended cycle day.

o. Variations of +/- 3 days of scheduled visits are permitted.

3.5 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.5.1 Criteria for removal from protocol therapy

- 3.5.1.1 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.
- 3.5.1.2 Patients require more than 2 dose reductions of carfilzomib.
- 3.5.1.3 Toxicity has not resolved after 2 weeks of withholding treatment or up to 3 weeks for infection related treatment
- 3.5.1.4 Grade 3non-blistering rash or blistering rash of any grade
- 3.5.1.5 Grade 3 neuropathy
- 3.5.1.6 Grade 3 hypersensitivity reaction
- 3.5.1.7 Patient completes the protocol as outlined in section 3.2
- 3.5.1.8 Progression of disease
- 3.5.1.9 Patient chooses to go off therapy
- 3.5.1.10 The principal investigator may remove patient from protocol therapy if deemed necessary due to medical conditions, compliance, etc.
- 3.5.1.11 Patient becomes pregnant.

3.5.2 Off-Study Criteria

- 3.5.2.1 Patient requests to be withdrawn from study
- 3.5.2.2 Death
- 3.5.2.3 Physician's determination that withdrawal is in the patient's best interest.

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site **(**http://intranet.cancer.gov/ccr/welcome.htm) main page must be completed and faxed to 301-480-0757.

All subjects must be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30am to 5:30pm EST Monday through Friday, excluding federal holidays. An off-study form will be supplied by the Coordinating Center, NCI CCR. Fax the completed off-study form to the CRO at 301-480-0757.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 TUMOR LYSIS SYNDROME

1. Hydration and Fluid Monitoring:

   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: 500 mL (250 mL before & 250 mL after carfilzomib) OR 1000 mL (500 mL before & 500 mL after carfilzomib) of normal saline or other appropriate IV fluid formulation must be given before *and* after each

carfilzomib dose during Cycle 1 D1 and D2. Total volume will be determined at the discretion of clinician and volume status of patient. If lactate dehydrogenase (LDH) or uric acid is elevated at Cycle 2, Day 1, then the recommended IV hydration should be repeated for Cycle 2. The goal of the hydration program is to maintain robust urine output, (e.g., ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.

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.

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

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. 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 Onyx as a Serious Adverse Event (SAE) through the normal process within 24 hours of the clinical site becoming aware of the event.

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

1. Subjects may receive RBC or platelet transfusions if clinically indicated.
2. 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 everyday 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.

4.4 HSV, VSV PROPHYLAXIS

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

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH STUDIES

1) Bone Marrow

Sampling Time Points of Bone Marrow correlative studies

	Baseline	Cycle 1 Day 2	During cycle 2-8 if CR achieved or at end of cycle 8 if no CR is achieved	During cycles 9-20 if CR is achieved or at end of Cycle 20 if no CR is achieved.	Progression of disease
Pathology/IHC	X		X	X	X
Multiparametric Flow Cytometry	X		X	X	X
FISH/Cytogenetics	X				X
Molecular pathology for light or heavy chain immunoglobulin rearrangement and/or KRas and NRas mutation analysis	X		X (optional)	X (optional)	X
CD138+ sorting/Gene expression profiling/microenvironment	X	X	X	X	X
Storage	X	X	X	X	X

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

b. Collection of bone marrow, sorting of bone marrow and storage of bone marrow samples is outlined in Appendix C and Section 5.2.1

c. 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 Katherine Calvo, MD, PhD. 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 Maryalice Stetler-Stevenson of the flow cytometry unit in the NCI Laboratory of Pathology

iii. FISH and cytogenetics: Interphase FISH/cytogenetics will be performed on patients enrolled in this protocol in the NCI Laboratory of Pathology Clinical Cytogenetics Unit under the direction of Dr. Diane Arthur.

iv. Cell Sorting, GEP profiling, and microenvironment interactions - Marrow aspirate will be sent to Adriana Zingone, MD, Ph D and sorted into CD 138 + and CD 138 – fractions.

- GEP profiling: CD138+ plasma cells will be purified from bone marrow aspirates harvested at each indicated time point. GEP will be performed in the laboratory of Adriana Zingone/Ola Landgren using the Affymetrix U133 Plus 2.0 microarray platform. Gene expression profiles will be analyzed to identify potential markers of early progression. Changes in selected genes will be confirmed by quantitative PCR if suggested to be related to risk of progression to MM. Additional genes may be analyzed for genetic sequence, including but not limited to the Ras pathway genes, and studies for their correlation with risk of progression to MM
- CD 138- fractions will be analyzed for microenvironment interactions such as cytokine profiling, miRNAs, etc. A fraction of CD138- cells will also be cultured to isolate bone marrow stromal cells for further analyses.
- Both fractions will be collected, batched, and entered into a biobank. See Section 5.2.1 for storage of bone marrow biobank.
- Aspirate samples may also undergo identification of downstream signaling targets, proteasome activity, and ubiquitination pathways on cell lysate or marrow aspirate.

2) Research Blood/Serum and Urine

a. 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:
    a. Baseline
    b. Days 2, 8 and 15 of Cycle 1
    c. 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
    d. Day 1 of every third cycle during cycles 9-20 (cycles 12, 15 and 18), and if patient achieves CR or at the end of cycle 20 if no CR is achieved.
    e. and at any time point if the patient has progression of disease.

b. The standard number of peripheral blood research tubes drawn for collection and storage at each of the above timepoints may include but are not limited to the following: one 7-8 mL serum tube, one 10 mL plasma heparinized tube, and one 10 mL EDTA tube.

c. 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 timepoints. Typical time points include:
    a. Baseline
    b. Day 2 of Cycle 1
    c. Day 1 of every cycle during cycles 2-8
    d. Day 1 of every third cycle during cycles 9-20 (cycles 12, 15 and 18)
    e. and at any time point if the patient has progression of disease. The amount of urine collected will be dictated by the number of experiments to be performed.

d. 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. Please page Dr. Figg's lab at 102-11964 for immediate pick-up. For any questions, contact the Clinical Pharmacology Program processing group in 10/5A09 at 301-594-6131 or 301-402-3622.

e. 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 Maryalice Stetler-Stevenson, MD.
- Subunit profiling and activity of circulating proteasomes by enzyme-like immunosorbent assay under the direction of Adriana Zingone, MD, PhD
- Apoptosis assays pre and post-carfilzomib to identify necrotic or late stage apoptotic cells will be performed by Adriana Zingone, MD, PhD
- Immunolocalization studies will be performed by Adriana Zingone MD, PhD
- 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.

3) Imaging

a. 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, and during cycles 9-20 if patient obtains CR or at the end of cycle 20 if no CR obtained. At PI discretion, patient may be asked to have an additional PET-CT at progression.

b. The radiation dose from the procedure will be a maximum of 4.1 rem per year; this is within the RSC guidelines of 5.0 rem per year for adults.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.2.1 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 IRB notification and an executed MTA.
- Bone marrow biopsies will be submitted in native condition to the NCI Laboratory of Pathology 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.
- For the purposes of storage, marrow aspirate will be assigned a unique number and cataloged. These research samples will be stored in the laboratory of Adriana Zingone/Ola Landgren of the Metabolism Branch, 301-435-5424 or in a temperature controlled, alarm secured nitrogen tank in the NCI Department of Hematopathology.

- 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.

5.2.2 Procedures for stored serum, peripheral blood, and urine specimens:

- See Appendix D for processing and storage procedures for Dr. Figg's lab.

5.2.3 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 report destroyed samples to the IRB if samples 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 will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples, or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the Center for Cancer Research of the NCI.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

6.1.1 Data will be prospectively collected and entered into the NCI C3D clinical trials database. Adverse events related to either carfilzomib or research procedures will be collected into the NCI C3D database. All data will be kept secure. Personal identifiers will not be used when collecting and storing data. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number

6.1.2 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

6.1.3 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. These records will serve as the primary source material that forms the basis for the research record. All relevant data will also be entered on a computer database from which formal analyses are done. 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.

6.1.4 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 Maryann Yancey, RN who will enter the data into the study database. Additional blood or tissue samples drawn on patients enrolled in this protocol between scheduled visits may be forwarded and entered into the database as well.

6.2 RESPONSE CRITERIA

6.2.1 Response assessments will be performed Day 1 of every cycle during Cycles 1-8 and every third cycle during Cycles 9-20: Cycles 12, 15 and 18.

6.2.2 Disease Parameters

- Patients who have a measurable serum or urine M-protein. A "measurable" serum M-protein is ≥ 1 g/dL and a "measurable" urine M-spike is ≥ 200 mg/24 hours. If patient does not have a "measurable" serum or urine M-protein, but has either a serum kappa or lambda FREE light chain of 10 mg/dL along with an abnormal kappa to lambda free light chain ratio, patient is considered to have "measurable" disease.
- 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.

6.2.3 Response Criteria adapted from International Myeloma Working Group Criteria for Multiple Myeloma[4]:

6.2.3.1 Evaluation of Response Criteria

- **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
- **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. <u>If the serum and urine M-protein are unmeasureable, a ≥90% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.</u>
- **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 unmeasureable, 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 baseline in:
  - 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 measureable 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 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
- Development of ≥ 5% plasma cells in the bone marrow
- Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, hypercalcemia

6.2.4 Progression-Free Survival

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

6.2.5 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.

6.3 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 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section 6.1.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

An abnormal laboratory value will be considered an AE 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.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

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 drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- 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.

- allergic bronchospasm requiring intensive treatment in an emergency room or at home
- blood dyscrasias
- convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse.
- A new diagnosis of cancer during the course of a treatment should be considered as medically important.
- Pregnancy

7.1.5 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.6 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.7 Protocol Deviation (NIH Definition)

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

7.1.8 Protocol Violation (NIH Definition)

Any change, divergence, or departure from the study procedures in an IRB-approved research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy or reliability of the study data.

7.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB REPORTING

7.2.1 NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

The Protocol PI will report to the NCI-IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Violations or Deviations
- All Unanticipated Problems

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review

The protocol PI will report to the NCI-IRB:

1. All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
2. All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
3. All Grade 5 events regardless of attribution;
4. All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that require a sponsor recommended change to the protocol or the consent form or in the opinion of the PI increases risks to study participants will need to be reported to the NCI IRB.

7.3 IND SPONSOR REPORTING CRITERIA

An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

7.4 FDA REPORTING CRITERIA

7.4.1 IND Safety Reports to the FDA (Refer to 21 CFR 312.32)

7.4.1.1 Expedited reporting to the FDA

The Sponsor will notify FDA via phone, fax, or email of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information. This will be followed with a written report within 15 days using the MedWatch Form 3500a.

The study Sponsor will notify FDA in writing of any suspected adverse reaction that is both serious and unexpected as soon as possible but no later than 15 calendar days after initial receipt of the information using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendars days after receiving the request.

The study Sponsor will also report expeditiously as above:

- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

7.4.1.2 Exclusions to expedited reporting to the FDA

The following events will not be reported in an expedited manner but will be included in the annual report:

- Pain due to disease
- Events associated with bone marrow biopsy that resolve as anticipated
- Events associated with anesthesia that resolve as anticipated

7.4.2 FDA Annual Reports (Refer to 21 CFR 312.33)

The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

7.4.3 Expedited Adverse Event Reporting Criteria to the IND Manufacturer

7.4.3.1 SAE Reporting to Onyx

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 Onyx DS 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 Onyx 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 emailed or faxed together to Onyx DS.

The primary and preferred method for communicating information (e.g. MedWatch Form 3500a SAE report forms, SAE Supplemental Forms, source documentation, etc.) from the site to Onyx DS is to the Onyx DS Adverse Events e-mail address: **adverse.events@onyx-pharm.com**

Documents may also be FAXED to: 800-783-7954

Sites may contact Onyx DS via email above or at 001-510-597-6501. During normal business hours, 8 A.M. to 5 P.M. Pacific Standard Time (PST), an Onyx DS team member will be available to answer the call. If a call occurs outside of normal business hours, this number accepts voicemail messages and will be checked on a daily basis.

7.4.3.2 Reporting Pregnancy to Onyx

If a subject or spouse or partner of a subject becomes pregnant while enrolled in this clinical trial or up to three months following administration of carfilzomib, Onyx Drug Safety must be notified within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy (See Onyx Drug Safety and Pharmacovigilance Contact information above). If the subject is pregnant, carfilzomib must be withheld.

Subjects, spouses, or partners will be followed through the outcome of the pregnancy. The Investigator will be required to report the results to Onyx Drug Safety.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

7.4.3.3 SAE Reporting to Celgene

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 Celgene as described below.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or 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 Celgene 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 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 Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene 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: drugsafety@celgene.com

7.4.3.4 Reporting Pregnancy to Celgene

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 Celgene 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 Celgene 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 Celgene 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 Celgene 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.

Celgene 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

7.5 DATA AND SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis 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. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations and violations will be immediately reported to the IRB using iRIS and if applicable to the Sponsor.

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.

7.5.2 Sponsor Monitoring Plan

This trial will be monitored by personnel employed by Harris Technical Services on contract to the NCI, NIH. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

At least 25% of enrolled patients will be randomly selected and monitored at least biannually or as needed, based on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

8 STATISTICAL SECTION

8.1 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 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 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.

8.2 Statistical Analysis of Secondary Endpoints

Secondary endpoints are duration of response and progression free survival. 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.

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

9 COLLABORATIVE AGREEMENTS

9.1 Agreement Type

There will be two CRADAs for this protocol, one with Onyx Therapeutics, Inc. for Carfilzomib and another with Celgene Corporation for Lenalidomide. The CRADAs were drafted based on PHS Intramural Clinical Trial-CRADA Template and are being reviewed by the companies. The final versions are pending approval.

10 HUMAN SUBJECTS PROTECTIONS

10.1 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[28]. Recent studies have shown that MM is preceded by MGUS and SMM.[9] 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 [1-2]. 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[28]. 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.

10.2 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

10.3 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[29]. 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.[30] Procedures required for obtaining samples/data for experimental purposes (venipuncture, urine collection, PET/CT scan 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.

10.4 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, and PET/CT scan is minimal and of limited risk compared to the knowledge gained by depth of response from disease monitoring.

10.5 Consent and Assent Process and Documentation

Informed consent will be obtained from all patients on this trial. There will be no minors enrolled < 18 years of age; therefore, assent is unnecessary. The informed consent contains all elements required for consent. In addition, the Principal Investigator or an associate investigator or member of the research team will discuss the protocol in detail with the patient and will be available to answer all patient questions to allow the patient to give informed consent.

11 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

11.1 CARFILZOMIB (IND # 112587)

11.1.1 Source:

Carfilzomib is provided to investigator by Onyx Therapeutics, Inc. under a CRADA

11.1.2 Toxicity:

Likely Side Effects: those occurring in more than 20% or more than 20 out of 100 persons who receive carfilzomib:

- Fatigue (tiredness)
- Nausea
- Anemia
- Shortness of breath (at rest or with exertion) which in rare cases may be life-threatening or resulting in death
- Upper respiratory tract infection
- Thrombocytopenia: Decreased platelet count which may lead to bleeding or bruising
- Diarrhea
- Mild decreases in renal function which are generally reversible
- Vomiting
- Fever
- Headache
- Constipation
- Neutropenia: Decreased WBC counts which may lead to a decreased ability to fight infection
- Swelling of arms or legs
- Cough
- Back pain

Less Likely Side Effects: those occurring in 5-20% or 5 to 20 out of 100 persons who receive carfilzomib:

- Loss of/or decreased appetite
- Blood chemistry and electrolyte alterations
- Pain, burning or irritation at the injection site
- Dizziness
- Inflammation of the liver (mild, reversible changes in liver function tests)
- Rash and/or Itching
- Pneumonia or other lower respiratory tract infections
- Flu-like symptoms such as fever, chills, or shaking that may occur at any time but are more likely to occur on the day of or the day after carfilzomib infusion.
- Insomnia (difficulty sleeping)
- Anxiety

- Confusion or changes in mental state
- Blurred or double vision
- Numbness, tingling, or decreased sensation in hands and/or feet
- Generalized pain
- Pain in the bones or joint pain
- Muscle spasm, pain, or weakness
- General weakness, or lack of energy or strength
- Abdominal pain, discomfort, or swelling
- Indigestion (upset stomach)
- Increase or decrease in blood pressure
- Urinary tract infection
- Nosebleeds
- Dehydration

Rare and/or Potentially Serious Side Effects: these have occurred in less than 5% or in less than 5 out of 100 persons who receive carfilzomib:

- Infusion reactions (which can occur during or shortly after carfilzomib infusion) including flushing or feeling hot, fever, shakes, nausea, vomiting, weakness, tightness in the chest, and low blood pressure , shortness of breath,
- Inflammation of the pancreas (pancreatitis)
- Kidney failure which can lead to dialysis
- Worsening liver function up to and including liver failure
- Decreased or worsening heart function including chest pain, abnormal heart rhythm, heart attack and heart failure (may have a life-threatening or fatal outcome).
- Allergic reaction including total body rash, hives, and difficulty breathing
- Blood clots in the leg or lungs
- Infections in the blood
- Tumor lysis syndrome (TLS)

11.1.3 Formulation and preparation:

Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®). Lyophilized Carfilzomib for Injection is stored in a refrigerator at 2°C–8°C. Water for injection is the only acceptable solution for reconstitution. After addition of the appropriate amount of water for injection and vigorous mixing, the solution is administered as an IV infusion. Vials are for single use. A volume of carfilzomib appropriate for a patient's dose will be added to 5% Dextrose Injection (D5W) in a sufficient amount to yield a volume to administer 100 mL (qs. 100 mL) in a polyvinyl chloride or polyolefin container.
For clinical use, Carfilzomib products will contain excess drug-containing fluid to compensate for product container and administration set priming volumes.

Before dispensing Carfilzomib products from the Pharmacy, an administration set suitable for a portable pump (e.g., Gemstar set 13758-28) will be attached, the administration set tubing will be primed with drug-containing fluid, air will be purged from the tubing (but not the product container), and the administration set will be capped with a Luer locking cap.

Lyophilized Carfilzomib for Injection is an investigational therapeutic agent provided in a single-dose vial as a sterile, lyophilized powder in the following dosages:

- 25 mg Single-Use Glass Vial / 8 pk Carton
  Each single-dose vial contains 25 mg of carfilzomib in a 20 mL labeled glass vial with an elastomeric stopper and Red flip-off lid. The product is supplied to the site in labeled carton(s) containing eight (8) single-use vials/carton and is shipped and stored between 2°C - 8°C (36°F - 46°F). Remove the Red flip-off lid on the vial and aseptically add 12 mL of Water for Injection, USP to the lyophilized drug. Gently invert the vial multiple times and let stand to yield a clear solution containing 2 mg/mL carfilzomib. After reconstitution as instructed, a maximum total of 12.5 mL deliverable volume containing 25 mg of carfilzomib can be withdrawn from the vial.
- 45 mg Single-Use Glass Vial / 6 pk Carton
  Each single-dose vial provides 45 mg of carfilzomib in a 30 mL labeled glass vial with an elastomeric stopper and Yellow flip-off lid. The product is supplied to the site in labeled carton(s) containing six (6) single-use vials/carton and is shipped and stored between 2°C - 8°C (36°F - 46°F). Remove the Yellow flip-off lid on the vial and aseptically add 22 mL of Water for Injection, USP to the lyophilized drug. Gently invert the vial multiple times and let stand to yield a clear solution containing 2 mg/mL carfilzomib. After reconstitution as instructed, a maximum total of 22.5 mL deliverable volume containing 45 mg of carfilzomib can be withdrawn from the vial.
- 60 mg Single-Use Glass Vial / 4 pk Carton
  Each single-dose vial provides 60 mg of carfilzomib in a 50 mL labeled glass vial with an elastomeric stopper and Blue flip-off lid. The product is supplied in labeled carton(s) containing four (4) single-use vials/carton and is shipped and stored between 2°C - 8°C (36°F - 46°F). Remove the Blue flip-off lid on the vial and aseptically add 29 mL of Water for Injection, USP to the lyophilized drug. Gently invert the vial multiple times and let stand to yield a clear solution containing 2 mg/mL carfilzomib. After reconstitution as instructed, a maximum total of 30 mL deliverable volume containing 60 mg of carfilzomib can be withdrawn from the vial.

11.1.4 Stability and Storage:

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

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. Prior to administration, all reconstituted drug should be equilibrated to room temperature. DO NOT FREEZE LYOPHILIZED OR RECONSTITUTED DRUG.

Diluted Drug Product
After dilution with D5W for clinical use, Carfilzomib should be stored under refrigeration. Diluted Carfilzomib is stable for a total of 24 hours.

11.1.5 Administration procedures:

Carfilzomib will be administered by intravenous infusion over 30-minutes via portable (ambulatory) pump. Care should be taken in placing and maintaining the product container at a level physically higher than the pump to avoid advancing air into the administration set tubing.

11.1.6 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

11.2 LENALIDOMIDE

11.2.1 Source:

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

11.2.2 Toxicity:

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 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

11.2.3 Formulation and preparation:

Lenalidomide will be supplied as capsules for oral administration. Celgene Inc. will provide lenalidomide 5, 10, 15 and 25 mg capsules for the Induction Phase of the protocol and for the Maintenance Phase (extended dosing phase).

11.2.4 Stability and Storage:

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

11.2.5 Administration procedures:

Celgene Corporation will supply Revlimid® (lenalidomide) to the Clinical Center Pharmacy to be dispensed to study participants at no charge through the RevAssist® 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**.**

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

11.3 DEXAMETHASONE

11.3.1 Source:

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

11.3.3 Formulation and preparation:

Oral Tablet (Scored): 4 mg

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

11.3.4 Administration procedures:

Oral: Administer with meals to decrease GI upset.

I.V.: Administer intravenously over 10 minutes.

11.3.5 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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13 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.
	Dead.	0	Dead.

14 APPENDIX B: Requirements for RevAssist

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

Requirements for RevAssist

- 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 Celgene 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 RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

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.

15 APPENDIX C: Bone Marrow Aspirate Collection, Sorting and Storage

Collection of Bone Marrow

- 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 CCR Hematology lab technician to be given to CCR Pathology department (1 mL will go to Hematopathology and 1 mL will be delivered to Irina Maric, MD for research assessing proteasomes). Reposition needle and, for cellular specimens, slowly 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.
- For aspirate specified for flow cytometry under the direction of Maryalice Stetler-Stevenson, 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 B1B58 (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 21/or CR reached between cycles 9-20 will be sent for plasma cell flow cytometry immunophenotyping at Maryalice Stetler-Stevenson's lab.
- For aspirate designated for sorting, GEP profiling, microenvironment studies, send remaining aspirate sample to Adriana Zingone, MD, PhD. Place aspirate sample in EDTA syringe immediately on ice. Transfer within 30 minutes of sampling to the lab for processing.
- For aspirate specified for cytogenetics/FISH, aspirate will be sent to Dr. Diane Arthur's Clinical Cytogenetics Laboratory Building10 Room 4B52.
- For aspirate specified assessing proteasomes: 1 mL will be delivered to Irina Maric, MD for research assessing proteasomes

16 APPENDIX D: Peripheral Blood and Urine Collection And Storage

Venipuncture

- Up to 100 mL of peripheral blood will be collected into heparinized tubes 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)
- timepoint (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.

Sample Data Collection:

- All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in the Patient Sample Data Management System (PSDMS) utilized by the CPP. This is a secure program, with access to the PSDM System limited to defined CPP personnel, who are issued individual user accounts. Installation of PSDMS is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All CPP personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.
- PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS 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.).

Sample Storage:

- 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 CPP and offsite at NCI Frederick Central Repository Services (Fisher Bioservices) 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 the PSDM System. 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 CPP. 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), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e. broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

- 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 the PSDMS. 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.