MSK PROTOCOL COVER SHEET

Carfilzomib, Lenalidomide, and Dexamethasone in Newly-Diagnosed Multiple Myeloma: A Clinical and Correlative Phase I/II Dose Escalation Study

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Primary Objective This is a phase I/II study to assess the safety and efficacy of maximum up to 12 cycles of combinational therapy with dexamethasone, lenalidomide, and higher doses of carfilzomib in newly diagnosed MM patients. Total number of cycles delivered will be determined by response status. The primary objective of the phase I study will be to determine the MTD of carfilzomib when used in combination with dexamethasone, and lenalidomide. The primary objective of the phase II study is to assess the rate of MRD negativity after completion of the combination therapy using multiparametric flow cytometry

Secondary Objective of both phase I/II:

1. To evaluate the rates of overall response (partial response (PR) or better), very good partial response (VGPR) or better, and complete response (CR) or stringent CR (sCR). See section 12.0 for response definitions.
2. To estimate overall and progression-free survival.
3. To compare MRD techniques of multi-parametric flow cytometry with next-generation sequencing and mass spectrometry.
4. To create a bone marrow and peripheral blood sample bank. These samples may be used to later evaluate biological activity of carfilzomib, lenalidomide, and dexamethasone. Potential analyses include sequencing and gene expression profiling on pre and post therapy bone marrow samples, identification of potential biomarkers (blood, urine, bone marrow aspirates), and evaluation of proteasome activity.

Patient Population

Newly diagnosed patients with histologically confirmed multiple myeloma.

Study Design

- Single arm, two-stage phase I/II trial of combination therapy (carfilzomib, lenalidomide, and dexamethasone [CRd]) for newly diagnosed multiple myeloma patients
- Each cycle consists of 28 days
- After 4 cycles of therapy, transplant eligible patients will undergo stem cell collection
- Pre- and post-treatment bone marrow biopsies will be obtained for confirmation of diagnosis and correlative studies
- Patients will receive maximum up to 12 cycles of induction combination therapy of CRd. Total number of cycles delivered will be determined by response status. Patients will also undergo evaluation for response at monthly intervals using traditional IMW uniform response criteria (Rajkumar. et al. Blood 2011) with SPEP, 24-hr UPEP (if applicable), serum free light chains (FLC), and immunofixation.
    - Patients with ≤PR at completion of 4 cycles, will stop therapy and be taken off protocol at completion of 4 cycles.

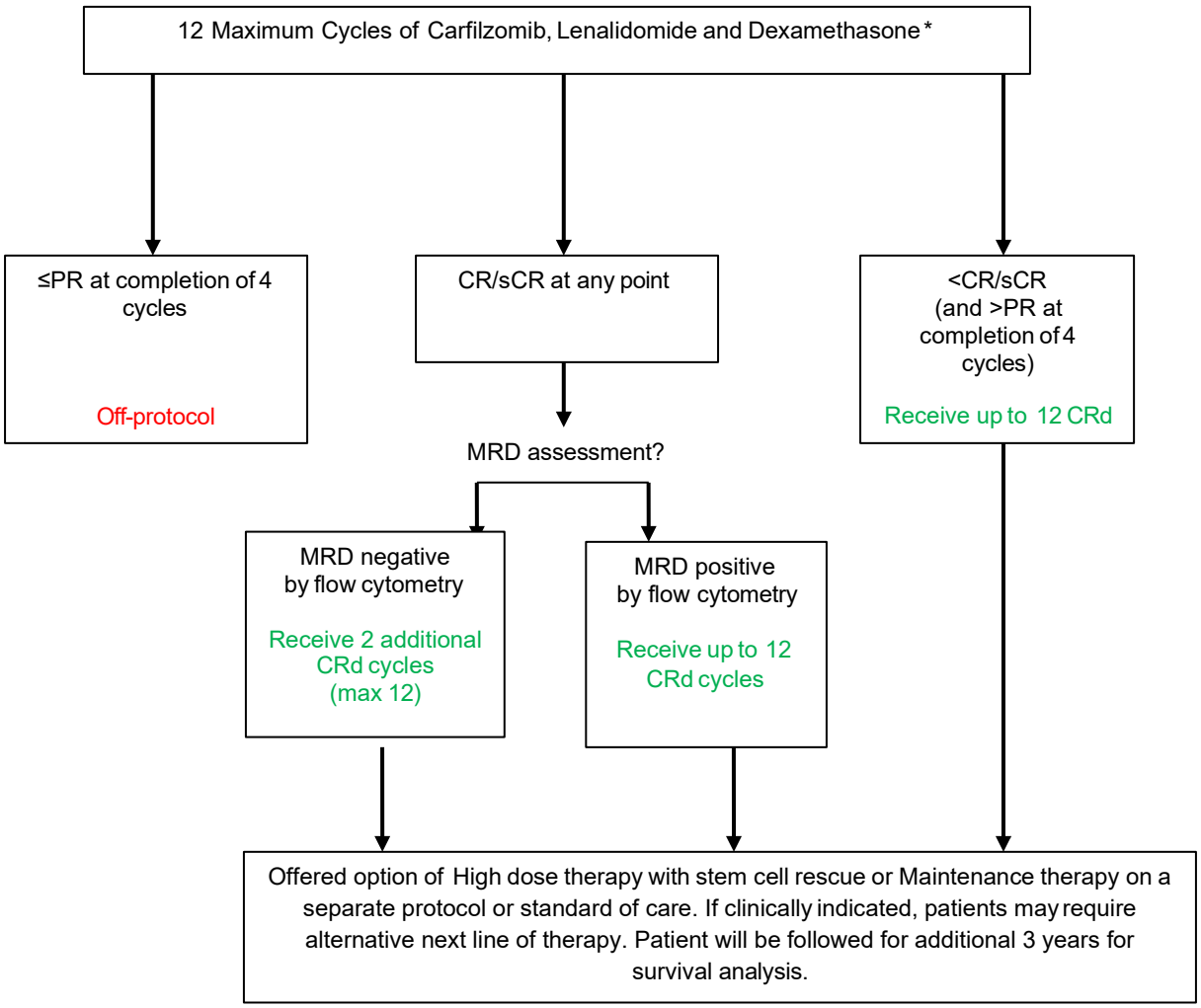
- For patients achieving >PR at end of 4 cycles, patients will continue to receive combination therapy with maximum up to 12 cycles.
    - Patients obtaining CR/sCR at any point during cycles in serum and urine will undergo MRD testing using multi-parametric flow cytometry.
        - Patients who attain minimal residual disease (MRD) negative status will stop treatment after 2 additional cycles (maximum 12 cycles).
        - Patients who are MRD positive will stop treatment at completion of 12 cycles. Patients converting from MRD positive status to negative status on subsequent MRD testing can stop after 2 additional cycles
    - Patients achieving <CR/sCR (and >PR at end of 4 cycles) will stop treatment at completion of 12 cycles.
- Upon completion of protocol therapy, patients will be encouraged to proceed onto maintenance therapy or high dose therapy with stem cell rescue under a separate treatment protocol or standard of care. If clinically indicated, patients may need alternative therapy.
- After completion of protocol therapy, patients will remain on study for an additional 3 years for survival analysis.

Treatment Plan (see schema below)

- Cycle 1 ONLY: Carfilzomib 20 mg/m^2 per dose, days 1 and 2; Carfilzomib 45 or 56 mg/m^2 per dose, days 8, 9, 15, and 16
- Cycles 2- up to 12: Carfilzomib 45 or 56 mg/m^2 per dose, days 1, 2, 8, 9, 15, and 16
- Cycles 1- up to 12: Lenalidomide 25 mg/day, days 1–21 every 28 days
- Cycles 1-4: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15, 16, 22, and 23
- Cycles 5- up to 12: Dexamethasone 10 mg/dose, days 1, 2, 8, 9, 15, 16, 22 and 23
- After receiving first 4 cycles, patients who are considered to be eligible for subsequent high dose therapy/autologous stem cell transplant (ASCT) will undergo autologous stem cell harvesting for potential use in the future. For patients who choose to undergo stem cell harvest, next cycle may be delayed for up to 7 weeks.
- If patients achieve > PR after completion 4 cycles, patients may receive additional combination therapy (maximum permissible 12 cycles). Patients may go onto receiving additional maintenance phase therapy with lenalidomide under a separate treatment protocol.
    - Patients obtaining CR/sCR and MRD negative status by flow cytometry will stop treatment after 2 additional cycles (maximum 12 cycles) delivered.
    - Patients obtaining CR/sCR and MRD positive status by flow cytometry will stop treatment after completing 12 cycles. Patients converting from MRD positive status to negative status on subsequent MRD testing can stop

after 2 additional cycles
  - Patients achieving <CR/sCR will stop treatment after completing 12 cycles.
- Patients ≤PR after completing 4 cycles will go off study therapy.
- Upon completion of protocol therapy, patients will be encouraged to proceed onto maintenance therapy or high dose therapy with stem cell rescue under a separate treatment protocol or standard of care. If clinically indicated, patients may need alternative therapy
- After completion of protocol therapy, patients will remain on study for an additional 3 years for survival analysis.

Schema



* After 4 or more cycles, patients considered transplant eligible will be recommended for stem cell collection. Stem cell collection is not part of the current protocol.

**For patients with non-evaluable samples at MRD assessments byflow cytometry, patients can opt for a repeat assessment or continue with up to 12 cycles of CRd therapy.

***Patients converting from MRD positive status to negative status on subsequent MRD testing can stop after 2 additional cycles

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

This is a phase I/II study to assess the safety and efficacy of up to12 cycles of combinational therapy with dexamethasone, lenalidomide, and higher doses of carfilzomib in newly diagnosed MM patients. The primary objective of the phase I study will be to determine the MTD of carfilzomib when used in combination with dexamethasone, and lenalidomide. The primary objective of the phase II study is to assess the rate of MRD negativity after completion of the combination therapy using multiparametric flow cytometry

Secondary Objectives of Phase I and II:

1. To evaluate the rates of overall response (PR or better), VGPR or better, and CR.
2. To estimate overall and progression-free survival.
3. To compare MRD techniques of multi-parametric flow cytometry with next-generation sequencing and mass spectrometry
4. To create a bone marrow and peripheral blood sample bank. These samples may be used to later evaluate biological activity of carfilzomib, lenalidomide, and dexamethasone. Potential analyses include sequencing and gene expression profiling on pre and post therapy bone marrow samples, identification of potential biomarkers (blood, urine, bone marrow aspirates), and evaluation of proteasome activity.

3.0 BACKGROUND AND RATIONALE

3.1 Introduction

Multiple Myeloma and Carfilzomib

Multiple myeloma is characterized by clonal proliferation of malignant plasma cells in the bone marrow, affecting an estimated 22,000 people in the US annually [1]; about 75,000 people are living with, or in remission from, multiple myeloma. Disease hallmarks include presence of monoclonal protein in serum or urine and features of end organ damage, including hypercalcemia, renal insufficiency, anemia, and bone lytic lesions [2]. Multiple myeloma remains incurable with an estimated median survival of 3-4 years with conventional therapies and longer with newer agents [3,4].

Proteasomes 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 [5]. Inhibiting proteasomes in malignant cells lead to buildup of ubiquinated proteins, resulting in eventual cell death. Such inhibitor effects likely extend beyond just a simple over-accumulation of cell waste. Rather, proteasome inhibitors also exert direct effects on the myeloma microenvironment and enable neoplastic cells to "re-direct" cell proliferation/apoptotic signaling while overcoming drug resistance mechanisms.

Carfilzomib (Cfz) 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[6-8]. In vitro models suggest carfilzomib has activity against bortezomib resistant myeloma cell lines[7]. Carfilzomib can also work synergistically with dexamethasone to enhance tumor cell death[7]. In the pivotal, phase II, noncomparative study of heavily pre-treated patients (n=266) with relapsed and refractory multiple myeloma, intravenous carfilzomib administered in 28-day cycles for up to 12 cycles produced an overall response rate of 23.7% in the response-evaluable patients[9]. The median duration of response was 7.8 months, the median progression-free survival was 3.7 months and the median overall survival was 15.6 months. An integrated analysis of 3 phase 2 studies with single-agent carfilzomib in patients with relapsed and refractory myeloma (N = 526) showed that the most common grade 3/4 adverse events (AEs) were thrombocytopenia (23%), anemia (22%), and lymphopenia (18%); peripheral neuropathy was 14% for any grade and 1.3% for grade 3 with no grade 4 events[10].

Carfilzomib in Combination with Lenalidomide and Dexamethasone

More recently, Jakubowiak et al published the results of a Phase 1/2 study in patients with newly diagnosed multiple myeloma where carfilzomib was administered in combination with lenalidomide (Revlimid®) and dexamethasone (CRd)[11]. No maximum tolerated dose (MTD) was reached. The maximum planned dose level (carfilzomib 36 mg/m^2) was expanded in phase 2 (n = 36). Grade 3/4 toxicities included hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%), and neutropenia (17%); peripheral neuropathy was limited to grade 1/2 (23%). After a median of 12 cycles (range, 1-25), 62% (N = 53) achieved at least near-complete response (nCR) and 42% stringent CR (sCR). Responses were rapid and improved during treatment. In 36 patients completing 8 or more cycles, 78% reached at least near CR and 61% stringent CR. With median follow-up of 13 months (range, 4-25 months), 24-month progression-free survival estimate was 92%.

At the National Cancer Institute, we recently published results of a phase II clinical and correlative study of CRd in patients with newly diagnosed MM patients[1]{Korde, 2015 #4573}. Patients were administered eight 28-day cycles of therapy including carfilzomib IV 20/36 mg/m^2 (based on prior Jakubowiak trial) on days 1, 2, 8, 9, 15, 16. After 8 cycles of CRd, all patients with stable disease (SD) or better receive cycles 9–20 of lenalidomide

maintenance 10 mg days 1–21. Of the 45 patients evaluable for toxicity and response, none reported ≥ grade 3 neuropathy. This finding stands in sharp contrast with bortezomib, which can be associated with sensory neuropathy in up to 80% of treated patients when used in combination with lenalidomide and dexamethasone[13]. The CRd regimen (using 36 mg/ m^2) resulted in rapid and deep responses with an overall response rate of 98% (n=42) and sCR/CR in 56% (n=25). The median time to sCR was 5 cycles (range 2-18).

Minimal Residual Disease Testing in Myeloma

In the past decade, multiple myeloma patients have reached deeper response rates with use of effective anti-myeloma therapeutics, immunomodulatory agents and proteasome inhibitors, approximating up to 75% patients achieving near-complete response (>90% decrease in monoclonal protein) or complete response (100% decrease in monoclonal protein){Kumar, 2008 #716}. In general, improved therapeutics and deeper response rates have resulted in improved overall survival of multiple myeloma patients across most age groups. As a result, there has been an increasing demand for the development of sensitive assays to detect minimal residual disease (MRD) in treated MM patients. In MM patients receiving autologous stem cell transplant, MRD-negative status using multi-parametric flow cytometry (MFC) is associated with improved progression free survival and overall survival. Similar studies using next generation sequencing methods for MRD have also been shown to be associated with improved outcomes in MM MRD-negative patients. In our prior study, among the 25 patients with CR/sCR that were assessed by MFC for immunophenotypic abnormal plasma cells; 25 out of 25 were negative for (MRD with an overall MRD negative rate of 25/43 (58)% (*2 patients did not have evaluable samples) using MFC. Using next generation sequencing molecular tests, the CR/sCR MRD negative rate was 13/33 (39%) (*12 patients did not have evaluable samples) (Sequenta platform). In patients with NDMM treated with CRd, 12-month progression-free survival for MRD-negative vs MRD-positive status by flow cytometry and next-generation sequencing was 100% vs 79% (95% CI, 47%-94%; $P < .001$) and 100% vs 95% (95% CI, 75%-99%; $P = .02$), respectively.

Minimal Residual Disease Platforms

A recent survey including 30 major institutions in the US found major heterogeneity in MRD testing of multiple myeloma by flow cytometry[16]. In brief, there was considerable variation in the number of bone marrow cells analyzed (events) and number of abnormal plasma cells needed to define the presence of MRD, which affects maximum possible sensitivity. The maximum detection sensitivity ranged from 0.0005% to 0.02%, a 100-fold difference in sensitivity. Also, the variation in antibodies studied and definition of an abnormal plasma cell by flow cytometry affected the ability to differentiate normal from neoplastic plasma cells.

In 2015, the Department of Laboratory Medicine developed, validated and implemented the 10-color flow cytometry platform in collaboration with the Myeloma Service and the International Myeloma Foundation. The MSK single tube 10-color flow cytometry platform demonstrates similar results to Euroflow and is already in use under clinical practice (publication submitted). Because there is currently no data available to compare

the sensitivity of the MSK model and molecular MRD assays, as a secondary endpoint, we will compare our 10-color flow cytometery platform against next generation sequencing and mass spectrometry. These studies will help us to better understand and further develop details of various MRD methods.

3.2 Proposed Study Investigation with Correlative Studies

Given the potent anti-myeloma activity of the CRd combination as demonstrated by rapid and deep remissions and the lack of a defined MTD, as a logical extension to the above mentioned studies, we propose a phase I/II investigation in newly diagnosed MM employing 2 escalated dose levels of carfilzomib at 20/45mg/m^2 and 20/56mg/m^2 in combination with lenalidomide and dexamethasone administered over a maximum 12 twenty-eight day cycles. These two dose levels were chosen based on information provided by Amgen Pharmaceuticals and based on phase 1 studies in relapsed-refractory MM showing the safety and efficacy of the drug as well as evidence of a dose-response relationship on multivariate modeling analysis[17-19].

After 4 cycles of treatment with CRd, transplant eligible patients will be encouraged to undergo autologous stem cell harvesting. Harvested stem cells will be stored for future use at time of disease relapse or progression. All patients will receive combination therapy with CRd. M-spikes and FLCs will be monitored every month. Patients achieving ≤PR after completion of 4 cycles of therapy will stop protocol therapy. Patients that are <CR/sCR (but >PR after 4 completed cycles) will receive up to 12 cycles of CRd. At any point during protocol, if patients achieve CR/sCR by serum and/or urine assessments[20], patients will undergo bone marrow biopsy to confirm CR per standard criteria. At work-up, if the bone marrow is found to be MRD negative by multiparametric flow cytometry, patient will receive 2 additional cycles of CRd (maximum 12 cycles). Patients that are CR/sCR but MRD positive by multiparametric flow cytometry will receive 12 cycles of CRd. The first pulled bone marrow sample will be sent for multi-parametric flow cytometry as a priority sample. Upon completion of protocol therapy, patients will be encouraged to proceed onto maintenance therapy or high dose therapy with stem cell rescue under a separate treatment protocol or standard of care. Some patients may need alternative therapy after completing protocol therapy. Collected bone marrow and peripheral blood samples will be processed and stored to create a sample bank used to later evaluate biological activity of carfilzomib, lenalidomide, and dexamethasone.

The study is powered to assess safety of higher doses of carfilzomib in combination with lenalidomide/dexamethasone **and** to evaluate MRD status. Our study is novel since no prior myeloma study has been designed to use MRD as the primary endpoint or used a response-adapted strategy based on MRD status. Secondary endpoints include evaluation of response rates, 3-year progression-free survival, 3-year overall-survival, and comparison of MRD platforms. Based on the rapidly evolving field with new powerful drugs, the anticipation is that MRD will become a new endpoint for future myeloma trials. MSK myeloma service is a global leader in this context.

3.3 Federal Regulations: The Privacy Rule

In the case of research repositories of tissue and biological specimens, the collection of such samples is treated as research under the Privacy Standards (67 Fed Reg 53231; HIPAA Privacy Rule and Public Health: Guidance from CGC and HHS). Under HIPAA, all subjects must agree to

sign research authorizations that describe the uses and disclosures of their protected health information, as well as informed consents that describe the risks and benefits of participating in the study. It is not acceptable to sign one or the other. Both documents must be signed by the subject to be considered a valid study participant (45 CFR 164.508(b)(3)).

The aim of informed consent is to educate potential research participants about the risks and benefits of the study, how confidentiality of records will be protected, and other elements outlined in 45 CFR 46 and 21 CFR 50 and 56. HIPAA requires an authorization that can be incorporated into an informed consent document if both the Privacy Rule and either the Common Rule or FDA regulation apply to the research study. If the health information is de-identified under the privacy standards (eliminating the 18 elements of PHI), then the Privacy Rule does not apply.

3.4 Office of Human Research Protections Guidance

The Office of Human Research Protections (OHRP, 1997) provides clarification, guidance, and oversight for research subject to the Common Rule. Research use of banked tissue or biological material is specifically addressed by an OHRP policy guideline. IRB oversight is recommended for the process of specimen acquisition into the repository as well as for the process of distributing samples to subsequent researchers and their local IRBs. OHRP suggests informed consent "should be as specific as possible" and include a "clear description" of the following basic elements: a) the operation of the cell repository; b) the specific types of research to be conducted; c) the conditions under which data and specimens will be released to recipient-investigators; and d) procedures for protecting the privacy of subjects and maintaining the confidentiality of data.

3.5 New York State Law

Under HIPAA, in instances where a state law is more stringent than the Privacy Rule, the state law is to be followed. In New York State, genetic test results (those that contain genetic information on inherited risk of disease) are confidential and cannot be disclosed to anyone without the written informed consent of the individual to whom the genetic test result relates (New York State Civil Rights Law §79-1(3)(a)). Genetic testing is defined by this law as:

> *any laboratory test of human DNA, chromosomes, genes, or gene products to diagnose the presence of a genetic variation linked to a predisposition to a genetic disease or disability in the individual or the individual's offspring; such term shall also include DNA profile analysis*…

According to §79-1(4)(a), anonymous samples may be genetically tested for Institutional Review Board (IRB)-approved research in which the anonymity of the samples is assured. For research genetic testing using human tissue stored in repositories, a general waiver of informed consent may be obtained (§79-1(2)(c)) if the individuals who supplied the samples "have given prior written informed consent for the use of their sample for general research purposes and did not specify time limits or other factors that would restrict use of the sample" (§79-1(9)(a)). The samples must be either permanently de-identified or coded such that the researcher performing the genetic test is unable to re-identify the specimens.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Patients with newly diagnosed MM will be enrolled on the Phase I/II study and treated with 3-drug combination of carfilzomib, lenalidomide, and dexamethasone.

4.2 Intervention

- Cycle 1 ONLY: Carfilzomib 20 mg/m^2 per dose, days 1 and 2; Carfilzomib 45 or 56 mg/m^2 per dose, days 8, 9, 15, and 16
- Cycles 2- up to 12: Carfilzomib 45 or 56 mg/m^2 per dose, days 1, 2, 8, 9, 15, and 16
- Cycles 1- up to 12: Lenalidomide 25 mg/day, days 1–21 every 28 days
- Cycles 1-4: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15, 16, 22, and 23
- Cycles 5- up to 12: Dexamethasone 10 mg/dose, days 1, 2, 8, 9, 15, 16, 22 and 23
- After receiving first 4 cycles, patients who are considered to be eligible for subsequent high dose therapy/autologous stem cell transplant (ASCT) will undergo autologous stem cell harvesting for potential use in the future. For patients who choose to undergo stem cell harvest, the next cycle may be delayed for up to 7 weeks.
- Patients will receive maximum up to 12 cycles of induction combination therapy of CRd. Total number of cycles delivered will be determined by response status.
    - Patients achieving ≤PR after completion of 4 cycles of therapy will stop protocol therapy.
        - For patients achieving >PR at end of 4 cycles, patients will continue to receive combination therapy with maximum up to 12 cycles.
        - Patients obtaining CR/sCR at any point in serum and urine will undergo MRD testing using multi-parametric flow cytometry.
            - Patients who attain minimal residual disease (MRD) negative status by flow cytometry will stop treatment after 2 additional cycles (maximum 12 cycles).
            - Patients who are MRD positive by flow cytometry will stop treatment at completion of 12 cycles. Patients converting from MRD positive status to negative status on subsequent MRD testing can stop after 2 additional cycles
        - Patients achieving <CR/sCR (and >PR at end of 4 cycles) will stop treatment at completion of 12 cycles.

4.2.1 Dose Limiting Toxicity

1. A DLT is defined as any of the below toxicities with attribution to one or more of the study drugs that occur during Cycle 1. Toxicities that occur in subsequent cycles will be handled through dose modifications but will not figure into the definition of MTD. All AEs should be

considered relevant to determining dose-limiting toxicities and to reporting unless the event can clearly be determined to be UNRELATED to the drug.

Non-hematologic

- ≥ Grade 2 neuropathy with pain
- ≥ Any Grade 3 toxicity (excluding nausea, vomiting, diarrhea, dexamethasone-induced hyperglycemia, electrolyte abnormalities not clinically significant and require no treatment except oral repletion lasting < 72 hous, or Grade 3 lenalidomide induced-maculopapular rash)
- ≥ Grade 3 nausea, vomiting, or diarrhea despite maximal antiemetic/antidiarrheal therapy lasting ≥ 7 days
- Grade 3 Creatinine increased ≥ 3x baseline or ≥ 4.0 mg/dL lasting ≥ 7 days
- ≥ Grade 3 fatigue lasting for ≥ 7 days
- Any non-hematologic toxicity requiring a dose reduction within Cycle 1 except for lenalidomide-induced maculopapular rash and dexamethasone-induced hyperglycemia
- Major bleeding toxicity defined as : ≥ Grade 3 hematoma, ≥ Grade 3 hemorrahage (specified organ- GI, renal, hematuria/bladder, lung, etc.) ≥ Grade 2 Intracranial hemorrhage.

Hematologic

- Grade 4 neutropenia (ANC < 0.5 x 10^9/L) lasting for ≥ 7 days
- Febrile neutropenia (ANC < 1.0 x 10^9/L with a fever ≥ 100.5°F)
- Grade 4 thrombocytopenia (platelets < 25.0 x 10^9/L) lasting ≥ 7 days despite dose delay
- Grade 3-4 thrombocytopenia associated with major bleeding
- Any hematologic toxicity requiring a dose reduction within Cycle 1

4.2.2 Dose Escalation

The trial will initially enroll 3 patients at the 45 mg/m^2 dose of carfilzomib and escalate to 56 mg/m^2 (Level 2) per table 4.2.2.2. Subjects need to receive all doses in first cycle to be eligible for next cohort dose escalation unless patient has a DLT. If excessive toxicity is observed at the starting dose (Level 1), the study include a further de-escalation dose of 36 mg/m^2 (Level -1)..

Table 4.2.2.1 Dose escalation table

Dose Escalation Schedule	
Dose Level	Carfilzomib *

Level -1	36
Level 1	45
Level 2	56
* Doses are stated as mg/m^2/dose; max BSA of 2.2 m^2	

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-
-
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Table 4.2.2.2 Dose escalation will follow the rules outlined in the Table below.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter up to 3 patients at the next dose level
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter up to 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. UP to three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

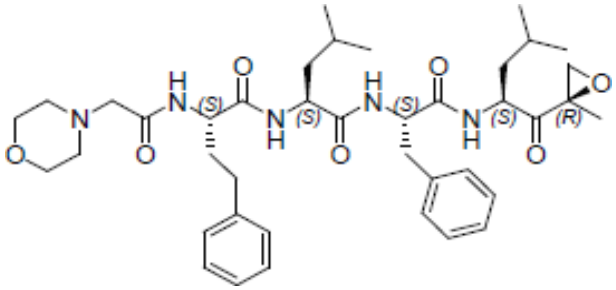
5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Carfilzomib (IND# 112587)

5.1.1 Scientific Background

Carfilzomib is a tetrapeptide ketoepoxide-based irreversible inhibitor developed by Amgen Pharmaceuticals, Inc. 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.

Chemical Structure of Carfilzomib



Carfilzomib is less reactive to non-proteasome proteases compared to bortezomib, likely contributing to lower levels of neuropathy and myelosuppression[11-13]. In vitro models suggest carfilzomib has activity against bortezomib resistant myeloma cell lines [12]. Carfilzomib can also work synergistically with dexamethasone to enhance tumor cell death[12]. A number of phase I and phase II studies are currently investigating carfilzomib toxicity and efficacy in MM.

5.1.2 *Formulation and Preparation of Drug*

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-□-cyclodextrin (SBE-□-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. Vials are for single use. After addition of the appropriate amount of water for injection and mixing, 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 in a polyvinyl chloride or polyolefin container is administered as an IV infusion .

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:

- *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.

5.1.2.1 *Inspection*

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

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

- DO NOT USE THE DRUG.
- Place the vial(s) into a plastic bag labeled as "Quarantined" with the date.
- Store labeled quarantined drug in a temperature-monitored refrigerator and ensure they are physically segregated from the drug that is available for use.
- Amgen will instruct the clinical site on how to proceed with quarantined vial(s).

5.1.2.2 *Calculation of Dose*

Each dose will consist of Carfilzomib for Injection administered on a mg/m^2 basis, and should be based on the patient's actual calculated body surface area (BSA).
The BSA should be calculated based upon the institution's practice and method of calculation should remain consistent throughout a subject's participation in the trial.

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

Dose adjustments do not need to be made for weight gains/losses of ≤ 20%.

5.1.2.3 *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.

5.1.2.4 *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 must be used on the day of reconstitution or else it must be destroyed. Prior to administration, all reconstituted drug should be equilibrated to room temperature. DO NOT FREEZE LYOPHILIZED OR RECONSTITUTED DRUG.

5.1.2.5 *Diluted Drug Product*

After dilution with D5W for clinical use, Carfilzomib should be stored under refrigeration.

5.1.3 Administration procedures:

Carfilzomib will be administered by intravenous infusion over 10 minutes for the 20 mg/m^2 dose and over 30-minutes for the 56 mg/m^2, 45 mg/m^2 and 36 mg/m^2 doses through a peripheral or central venous access device 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.

If the patient has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration.

5.1.4 Incompatibilities:

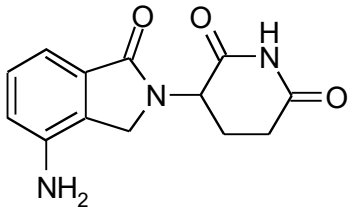
In an in vitro study using human liver microsomes, carfilzomib showed modest direct and time-dependent inhibitory effect on human cytochrome CYP3A4/5. Given that the clearance of carfilzomib likely occurs extrahepatically via the activity of epoxide hydrolase and peptidase activities, the clinical relevance 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.

5.2 Lenalidomide

5.2.1 Scientific Background

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



The mechanism of action of lenalidomide remains to be fully characterized. Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against MM. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in MM cell lysis. In addition, lenalidomide has direct activity against MM and induces apoptosis or G1growth arrest in MM cell lines and in MM cells of patients resistant to melphalan, doxorubicin and dexamethasone. Revlimid® is approved in combination with dexamethasone for the treatment of patients with MM that have received at least one prior therapy.[17,18] The drug has also been studied in newly diagnosed patients in combination with low-dose dexamethasone, as well as with bortezomib and dexamethasone as mentioned earlier.[19,8]

5.2.2 Forumulation and Preparation of Drug

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 extended dosing phase(s).

5.2.3 Stability and Storage:

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

5.2.4 Administration procedures:

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the REMS® program. Bottles will contain a sufficient number of capsules for one cycle of dosing; no more than a one-month supply of lenalidomide may be dispensed at one time.

5.2.5 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

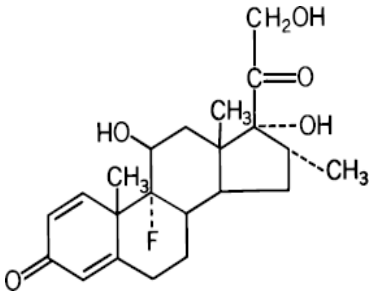
Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in MM patients receiving lenalidomide with dexamethasone

5.3 Dexamethasone

5.3.1 Preparation, Handling, Storage

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally-occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.

The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. The empirical formula is $C_{22}H_{29}FO_5$ and the structural formula is:



Dexamethasone is stable in air and almost insoluble in water.

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 2 or 4 mg tablets (commercially) for oral administration. Each tablet contains dexamethasone as the active ingredient, and the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch. The tablet shell may contain the following: D&C Yellow 10, FD&C Yellow 6, and/or FD&C Blue 1.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Dexamethasone should be stored at controlled room temperature, 68-77◦F (20-25◦C) and not frozen, and according to label requirements. Dexamethasone should be handled by trained pharmacy staff. The use of gloves and other appropriate protective clothing is recommended as necessary.

Dexamethasone supply will be obtained through commercial supply.

Dexamethasone is an oral drug, and does not require specific preparation details.

At the end of the study, unused supplies of dexamethasone should be destroyed and documented according to institutional policies.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

6.1 Subject Inclusion Criteria

- Newly diagnosed patients with histologically confirmed MM based on the following criteria:
  - Clonal plasma cells in the bone marrow
  - 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
    - Involved serum immunoglobulin free light chain > 10 mg/dL AND abnormal kappa/lambda ratio

- Evidence of underlying end organ damage and/or myeloma defining event attributed to underlying plasma cell proliferative disorder meeting at least one of the following:
  - Hypercalcemia: serum calcium >0.25 mmol/L (> 1 mg/dL) above upper limit of normal or ≥ 2.75 mmol/L (11 mg/dL)
  - Anemia: hemoglobin value <10 g/dL or > 2 g/dL below lower limit of normal
  - Bone disease: ≥ 1 lytic lesions on skeletal X-ray, CT, or PET-CT. For patients with 1 lytic lesion, bone marrow should demonstrate ≥10% clonal plasma cells
  - Clonal bone marrow plasma cell percentage ≥60%
  - Involved/un-involved serum free light chain ratio ≥100 and involved free light chain >100 mg/L.
  - > 1 focal lesion on magnetic resonance imaging study (lesion must be >5 mm) in size

- Creatinine Clearance ≥ 60 ml/min. CrCl can be measured or estimated using Cockcroft-Gault method

- Age ≥ 18 years at the time of signing the informed consent documentation

- Eastern Cooperative Oncology Group (ECOG) performance status 0-2

- Absolute neutrophil count (ANC) ≥ 1.0 K/uL, hemoglobin ≥ 8 g/dL, and platelet count ≥ 75 K/uL, unless if cytopenias are deemed to be due disease at discretion of clinical investigator. Transfusions and growth factors are permissible.

- Adequate hepatic function, with bilirubin < 1.5 x the ULN, and AST and ALT < 3.0 x ULN.

- All study participants must be able to tolerate one of the following thromboprophylactic strategies: aspirin, low molecular weight heparin or warfarin (coumadin) or alternative anti-coagulant.

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

- 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.

†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).

6.2 Subject Exclusion Criteria

- Patients receiving >1 cycle of prior treatment or concurrent systemic treatment for multiple myeloma
    - Treatment of hypercalcemia or spinal cord compression or aggressively progressing myeloma with current or prior corticosteroids is permitted
    - Bisphosphonates are permitted
    - Concurrent or prior treatment with corticosteroids for indications other than multiple myeloma is permitted
    - Prior treatment with radiotherapy is permitted
    - Prior treatment for smoldering myeloma is permitted with a washout period of 4 weeks from last dose. Smoldering patients previously treated with carfilzomib are excluded.

  - Patients with measurable disease who received up to one cycle of any therapy within 60 days with a washout period of 4 weeks from last dose (on a trial or outside a trial) are eligible

- Plasma cell leukemia
- POEMS syndrome
- Amyloidosis
- Pregnant or lactating females. Becase there is a potential risk for adverse events nursing infants secondary to treatment of the mother with carfilzomib in combination with lenalidomide. These potential risks may also apply to other agents used in this study.
- Uncontrolled hypertension or diabetes
- Active hepatitis B or C infection
- Known or suspected HIV or serologically positive
- Has significant cardiovascular disease with NYHA Class III or IV symptoms, EF≤40% or hypertrophic cardiomyopathy, or restrictive cardiomyopathy, or myocardial infarction within 6 months prior to enrollment, or unstable angina, or unstable arrhythmia as determined by history and physical examination. Echocardiogram will be performed during screening evaluation.
- Moderate or severe pulmonary hypertension defined as PASP > 50mm Hg. For those patients where PASP is indeterminate, moderate to severe symptoms of pulmonary hypertension (World Health Organization functional assessment class III or IV) will be used to determine exclusion criteria.
- Has refractory GI disease with refractory nausea/vomiting, inflammatory bowel disease, or bowel resection that would prevent absorption of oral agents
- Uncontrolled intercurrent illness including but not limited to active infection or psychiatric illness/social situations that would compromise compliance with study requirements
- Significant neuropathy ≥Grade 3 or Grade 2 neuropathy with pain at baseline
- Contraindication to any concomitant medication, including antivirals or anticoagulation.
- Major surgery within 3 weeks prior to first dose

7.0 RECRUITMENT PLAN

This study will be conducted at MSKCC. Efforts will be made to ensure that women and minority groups are adequately represented in this trial. Internally, an effort will be made to position this protocol for patients that demonstrate high-risk prognostic features, so as not to conflict with other ongoing newly-diagnosed multiple myeloma studies. All patients will be seen by MSKCC myeloma physicians and associated MSKCC co-investigators, enrolled and registered at MSKCC. All co-investigators agree to follow the treatment in the protocol and to conduct the proposed investigation according to recognized principles of good clinical practice. Participation is voluntary. Each patient must be informed about the neoplastic nature of his/her disease and willingly consent to participation in this study. Every patient will be informed of the procedures to be followed, the potential benefits, side effects, risks, and discomforts of the trial and of potential therapeutic alternatives. All participants will be required to sign statements of informed consent and research authorization that conform to FDA, IRB and HIPAA guidelines. Informed consent will be documented by the use of a written consent form that has been approved by the MSKCC IRB.

8.0 PRETREATMENT EVALUATION

- A complete history and physical examination with documentation of measurable disease and assessment of performance status using the ECOG scale must be performed within 4 weeks prior to study entry
    - Patients will be evaluated for baseline neuropathy. Patients with grade 2 with painful neuropathy or grade 3 and higher will be excluded.

<u>The following laboratory tests will be completed within 4 weeks prior to study entry</u>

- CBC with differential and reticulocyte count
- Chem 14, Magnesium, and Phosphate and eGFR determination
- Uric acid, LDH, and Beta-2 Microglobulin
- PT, PTT
- Serum protein electrophoresis (SPEP) and immunofixation to assess for presence and quantity of monoclonal protein (M-protein)
- 24 hour urine sample for protein electrophoresis (UPEP) and immunofixation to assess for monoclonal protein in the urine (Bence-Jones proteinuria) at baseline.
- Serum free light-chain studies, determined using the FreeliteTM assay system
- Quantitative immunoglobulins
- Viral serologies
    - Hepatitis B surface antigen
    - Anti-Hepatitis C (HCV) antibody. If positive, will follow with HCV RNA PCR
- Review of bone marrow core biopsy and aspirate.
- Serum or urine pregnancy test in women of child-bearing potential.
- 12-lead EKG
- Echocardiogram – 2D Echo or strain echo

Research and clinical laboratory tests to be performed within 4 weeks of study entry and prior to starting therapy

- Bone Marrow
  - Histopathological evaluation on bone marrow aspirate and biopsy
  - Immunophenotyping of aberrant clonal plasma cells by multiparametric flow cytometry.
  - Immunoglobulin heavy and/or light chain rearrangement.
  - Interphase FISH/cytogenetics
  - To create a bone marrow and peripheral blood sample bank of whole BM lysate, CD 138+ fractions and CD 138- fractions cell sorting with subsequent correlatives on both fractions. These samples may be used to later evaluate biological activity of carfilzomib, lenalidomide, and dexamethasone. Potential analyses include sequencing and gene expression profiling on pre and post therapy bone marrow samples, identification of potential biomarkers (blood, urine, bone marrow aspirates), and evaluation of proteasome activity.

- Peripheral Blood/Urine
  - Peripheral blood and urine samples for storage and establishing a biobank.
  - Immune cells – including, but not limited to T cells (CD4 and CD8), LGL, and NK cells.

Imaging (FDG/PET/CT scan) within 4 weeks of study entry and prior to starting therapy

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]-fludoeoxyglucose 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. 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 2.1 rem per year; this is within the RSC guidelines of 5.0 rem per year for adults.

PET-CT performed within the 4 weeks at an outside institution can be acceptable as baseline study as long as films are forwarded to the Department of Radiology for an official MSKCC reading

9.0 TREATMENT/INTERVENTION PLAN

Patients who have signed the consent form and are deemed eligible for this clinical trial will start therapy with carfilzomib, lenalidomide and dexamethasone (CRd) with the following schedule:

- Length of cycle: 28 days. Treatment window for day 1 of start of each cycle is +/- 7 days. Treatment window for intra-cycle carfilzomib doses is + /- 3 days.
- These cycles will consist of:
    - Carfilzomib
        - Cycle 1: 20 mg/m^2 IV infusion over 10 minutes on days 1 and 2, then 45 or 56 mg/m^2 IV infusion over 30 minutes on days 8, 9, 15, and 16 depending on the assigned dose level
        - Cycle 2 - up to 12: 45 or 56 mg/m^2 IV infusion over 30 minutes on days 1, 2, 8, 9, 15, and 16
    - Lenalidomide
        - Cycle 1 - up to 12: 25 mg oral days 1-21 of 28-day cycle
    - Dexamethasone
        - Cycle 1-4: 20 mg oral or IV on days 1, 2, 8, 9, 15, 16, 22, and 23
        - Cycle 5 - up to 12: 10 mg oral or IV on days 1, 2, 8, 9, 15, 16, 22, and 23

9.1 Cycle 1 adjustments

In Cycle 1, the following adjustments to the dosing schema will be implemented:

- Per FDA label recommendations and standard dosing in previous trials, carfilzomib will be given at a lower dose of 20 mg/m^2 on Days 1 and 2 of Cycle 1. Initiating carfilzomib at higher doses than 20 mg/m^2 may increase risk of cytokine release-like syndrome.
- Hydration will be administered prior and subsequent to carfilzomib dosing at the clinical discretion of the investigator or per MSKCC institution standard care practice.

9.2 Dose Modifications

9.2.1 Dose Reductions for Lenalidomide

	Lenalidomide
Baseline dose	25 mg
One level dose reduction	20 mg
Two level dose reduction	15 mg
Three level dose reduction	10 mg
Four level dose reduction	5 mg

9.2.2 Dose Reductions for Carfilzomib

	Carfilzomib DL -1	Carfilzomib DL 1	Carfilzomib DL 2
Baseline dose	36 mg/m^2	45 mg/m^2	56 mg/m^2
One level dose reduction	27 mg/m^2	36 mg/m^2	45 mg/m^2
Two level dose reduction	20 mg/m^2	27 mg/m^2	36 mg/m^2

If more than 2 dose reductions are required with Carfilzomib, study treatment will be discontinued and the patient will go off therapy. De-escalation of carfilzomib occurring in patients during first cycle (DLT window) of phase I will count as a DLT.

9.2.3 Dose Reductions for Dexamethasone

	Dexamethasone Cycles 1-4	Dexamethasone Cycles 5-10
Baseline dose	20 mg	10 mg
One level dose reduction	10 mg	4 mg
Two level dose reduction	4 mg	0 mg
Three level dose reduction	0 mg	

9.3. Hematologic Toxicity

9.3.1 On day 1 of each new cycle, patients must meet the following criteria:

- ANC ≥ 1.0 x 10^9 /L
- AST and ALT < 5 x ULN
- Platelet count ≥ 50 x 10^9 /L

9.3.2 If these conditions are not met on Day 1 of a new cycle:

- The next cycle of treatment will not be initiated until the above conditions (section 9.3.1) are met. If ANC and platelet counts do not satisfy the requirements above after 2 weeks of withholding treatment, the subject will go off therapy. Transfusions and growth factors are permissible after cycle 1.
- For patients not meeting day 1 criteria (section 9.3.1) for two cycles (non-consecutive), the study drug dose(s) will be modified for the next cycle based on dose reduction tables of section 9.2.

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

Thrombocytopenia	**Lenalidomide**	**Carfilzomib**
Fall to < 25 x 10^9/L	Hold both Lenalidomide and Carfilzomib, follow CBC at least weekly or more frequently if clinically indicated. 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 at least weekly or more frequently if clinically indicated. 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 at least weekly or more frequently if clinically indicated.	
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 at least weekly or more frequently if clinically indicated.	
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.

9.4 Non-Hematologic Toxicities Requiring Dosing Modifications

9.4.1 Any ≥Grade 3 toxicity require appropriate study drug to be held until resolved to Grade 1 or baseline (unless specified below in tables 9.4.4) prior to resuming therapy or initiating next cycle. Investigator will determine which drug will be held based on side effect profile and clinical judgment. If therapy has been held for more than 2 weeks due to non-hematologic toxicity, the patient will be removed from protocol therapy.

9.4.2 Protocol therapy will be withheld for patients who require treatment of Grade 3 infection. If therapy has been held for more than 3 weeks due to treating a grade 3 infection, the patient will be removed from protocol therapy.

9.4.3 For patients experiencing ≥grade 3 toxicity (unless specified below in tables 9.4.4), subsequent doses will be reduced at next dose level (according to the tables in section ***9.2***) if the adverse event was deemed to beattributed to study drugs. If the adverse event was deemed to be unrelated to study drugs, the patient may continue the full dose.

9.4.4 Electrolyte or metabolic abnormalities that are reversible with electrolyte replacement within 72 hours or < grade 3 infections that can be controlled by appropriate therapy are exempt from holding treatment or dose modifications.

Lenalidomide Toxicities	**Specific 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.
Infection (≥Grade 3)	Hold therapy, treat underlying infection. Remove patient from therapy if treatment of grade 3 infection persists for more than 3 weeks.

Carfilzomib Toxicities	Specific 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, clinically controllable (see below) or return to baseline. In patients with preserved EF, if symptoms are controllable by fluid management measures, patients may continue at current carfilzomib dose level. In patients with preserved EF but symptoms are not controllable by fluid management measures, carfilzomib should be dose reduced at next dose level. Any patient with symptomatic Class III or IV Heart failure and ejection fraction decrease from baseline, will stop therapy and go off protocol.
Hypertension (uncontrollable by medications, hypertension emergencies, or >3 episodes of hypertension urgencies)	Hypertension uncontrollable by medications or >3 episodes of hypertension urgencies – hold carfilzomib and decrease to next dose level. Hypertension emergecy – stop therapy and go off protocol
Myocardial infarction	Any patient experiencing myocardial infarction will stop therapy and go off protocol

9.5 Monitoring

9.5.1 Routine labs (CBC, chemistry panel 14, LDH, magnesium, uric acid, phosphate) will be performed on Day 1, 2, 8, 15, and 22 of cycle 1, Day 1 of each cycle thereafter, end of therapy, and 1-year and 3-year after end of therapy. Myeloma tests include serum protein electrophoresis, serum immunofixation, beta-2 microglobulin, quantitative immunoglobulins and serum free light chains assay will be performed at baseline, Day 1 of each cycle, end of therapy, and 1-year and 3-year after end of therapy. Serum Lymphocyte subsets will be performed at baseline, Day 1 of cycle 4, and end of treatment. Routine labs, myeloma labs, and lymphocyte subsets can be performed 24 hrs in advance.

9.5.2 For patients with intial baseline 24-hr UPEP samples demonstrating ≥100 mg/24 hrs, patients with continue to have 24-hr UPEP samples day 1 of each cycle. Once 24-hr UPEP is <100 mg/24 hrs, patient can have random UPEP with IFE until achieving negativity. If initial baseline 24-hr UPEP sample is IFE positive and/or <100 mg/24, patients can have random UPEP samples with IFE until achieving negativity. Once random UPEP and IFE is negative, no further urine samples are needed (unless patient's disease is primarily measurable by 24 hr urines i.e. oligosecretory/hyposecretory)

9.5.3 Patients will have clinic visits with H&P or standard progress notes assessing for toxicity/side effects on Day 1 of each cycle, end of therapy, 1-month after end of therapy, 1-year after end of therapy and 3-year after end of therapy. Treatment window for day 1 of start of each cycle is +/- 7 days. Treatment window for intra-cycle carfilzomib doses is +/- 3 days.

9.5.4 At CR/sCR or end of therapy, routine labs (CBC, chemistry panel 14, LDH, magnesium, uric acid, phosphate), myeloma specific tests - serum protein electrophoresis, serum immunofixation, beta-2 microglobulin, quantitative immunoglobulins and serum free light chains assay, lymphocyte subsets, 24-hr urine sample for protein electrophoresis (UPEP) and immunofixation to assess for monoclonal protein in the urine (Bence-Jones proteinuria). A bone marrow aspirate will also be performed to assess the status of minimal residual disease by flow cytometry (Sample sent will be the first bone marrow "pull"). Patient will have clinic visit (relevant clinical laboratorie and H&P) 1 month after completing combination therapy to undergo assessment of toxicities/adverse events.

9.5.5 Patients will have an EKG and echocardiogram (2-D or strain scho) performed at baseline and after completion of 4 cycles of therapy. ***Outside echocardiograms are permissable***

9.5.6 Patients will have FDG-PET-CT at baseline, end of therapy or upon suspicion of progressive disease as clinically indicated.

9.5.7 PFS and OS data will be collected for patients.

9.6 After Protocol Therapy

9.6.1 Upon completion of protocol therapy, patients will be encouraged to proceed onto maintenance therapy or high dose therapy with stem cell rescue under a separate

treatment protocol or standard of care. If clinically indicated, patients may need additional alternative therapy.

9.6.2 After completion of protocol therapy, patients will remain on study for an additional 3 years for survival analysis.

CONCOMITANT MEDICATIONS/MEASURES

TUMOR LYSIS SYNDROME

Hydration and Fluid Monitoring

a) Oral hydration: For patients deemed at risk for TLS or dehydration, oral hydration may be considered (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. Compliance must be reviewed with the subject and documented by the site personnel prior to initiating treatment with carfilzomib; treatment is to be delayed or withheld if oral hydration is not deemed to be satisfactory.
b) IV hydration: IV hydration will be administered per MSKCC institutional standards and can be adjusted at the clinical discretion of the investigator.

Laboratory Monitoring

1) Appropriate basic metabolic panel chemistries, including creatinine for day 1 of each cycle and days 1, 8, and 15 of cycle 1, and complete blood counts (CBC) with platelet count should be obtained. Labs may be drawn 24 hrs prior to receiving treatment.
2) Subjects with laboratory abnormalities consistent with lysis of tumor cells -fold increase, (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

Clinical Monitoring

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

Management

1) 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.

Optional medication for high-risk TLS patients

1) 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. At this point, the investigators do not anticipate the need for using rasburicase. Subjects who do not tolerate allopurinol should be discussed with the Lead Principal Investigator.

BONE DISEASE/EXTRAMEDULLARY DISEASE

1) Radiation therapy: Subjects may receive limited local radiation for treatment of uncontrolled pain, cord compression, vertebral instability/impending fracture, etc.
2) Kyphoplasty/Vertebroplasty: Subjects may receive kyphoplasty/vertebroplasty for symptomatic vertebral compression fractures.
3) Bisphophonate therapy: Approved bisphophonate therapy (zoledronic acid or pamidronate) is allowed. Patients will be monitored for renal function and osteonecrosis of the jaw. Patients may require prior evaluation from dental specialist before instituting bisphosphonates.

HYPERCALCEMIA

Patients may receive treatment for hypercalcemia including hydration, bisphophonates, furosemide, steroids, calcitonin, etc.

TRANSFUSIONS/GROWTH FACTORS

1) Subjects may receive RBC or platelet transfusions if clinically indicated.
2) Subjects may receive supportive care with erythropoietin or darbopoetin.
3) Colony-stimulating factors may be used if neutropenia occurs.
4) Growth factors and transfusions should not be administered prophylactically during cycle 1 unless clinically indicated.

ANTI-COAGULATION

Oral Aspirin 81 mg or 325 mg or suitable alternative anti-coagulation for thrombotic prophylaxis every day for the duration of their participation in the study.

HSV, VSV, PCP PROPHYLAXIS

Oral Valacyclovir of 500 mg daily or suitable alternative of Acyclovir throughout all cycles in which carfilzomib is given.

If CD4 count </= 200 /uL, PCP Prophylaxis with Bactrim/Pentamidine/Dapsone or suitable alternative should be considered by investigator unless there is a contraindication.

ANTI-EMETIC PROPHYLAXIS

Palonosetron 250 mg should beadministered on day 1, 8, and 15 but can be held at the discretion of the treating investigator.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Study	Pre-Treatment	Induction Treatment								End of therapy[i]	Follow-up	
		Cycle 1					Cycles 2- up to 12				1 month after end of therapy [i,l]	1-year and 3-year after end of therapy
		Day 1	Day 2	Day 8	Day 15	Day 22	After completing 4 cycles	Day 1[l]	CR/sCR reached			
Medical Record Review	x									x	x	x
H&P with blood pressure	x							x		x	x	x[m]
Echo + EKG	x						x[n]					
ECOG	x							x		x		
Informed Consent	x											
Viral Studies[b]	x											
Register for RevAssist	x											
Routine Labs[a]	x	x	x	x	x	x		x		x		x[m]
Lymphocyte subsets	x							x[a] (only C4D1)		x		
Myeloma tests[f,j]	x[f,j]							x[f,j]		x[f,j]		x[m]
Urine for UPEP and IFE [j]	x[j]							x[j]		x[j]		x[m]
Pregnancy Test[c]	x[c, d]	x[d]	x[d]	x[e]	x[e]	x[e]		x[c]			x[e]	
Research Blood/Urine	x		x	x	x	x		x	x	x		x[m]
Bone Marrow/Aspirate	x[g]								x[h]	x[h]		x[m]
FDG PET-CT[k]	x									x		

Adverse Events/Toxicity		**x**						**x**		**x**	**x**	

a. Routine tests include CBC, reticulocyte count, Chem 14, magnesium, phosphate, uric acid, eGFR determination and LDH. Reticulocyte count will only be performed at baseline, day 1 of every cycle, and end of therapy. PT and PTT will only be performed at baseline. Peripheral blood lymphocyte subsets at baseline, C4D1, and end of therapy. In addition, a CBC must be performed on days 8 and 15 of every cycle. Labs can be performed 24 hrs in advance.
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 co nsecutive 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 A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
f. Myeloma tests include serum protein electrophoresis, serum immunofixation, 24-hr urine electrophoresis, urine immunofixation, serum free light chains, quantitative immunoglobulins, beta-2 microglobulin. Labs can be performed 24 hrs in advance.
g. Bone marrow aspiration and biopsy will be sent for histopathology, flow cytometry, FISH/cytogenetics, heavy/light chain immun oglobulin rearrangement,. Aspirate lysate will also be sent for cell sorting into CD 138- and + fractions and whole bone marrow lysate for HOTB storage so molecular profiling with GEP and DNA-based sequencing at baseline can be performed as correlative work.
h. Bone marrow aspirate and biopsy can be performed +/- 21 days of intended cycle day or achievement of CR/sCR. The first pull bone marrow aspirate will be sent for MRD testing for Multiparametric flow cytometry. Bone marrow aspirate and biopsy will be sent to evaluate for histopathology, flow cytometry (bone marrow immunophenotyping of plasma cells), heavy/light chain immunoglobulin rearrangemen t. Aspirate lysate will also be sent for cell sorting into CD 138- and + fractions and whole bone marrow lysate for HOTB storage so molecular profiling with GEP and DNA-based sequencing at baseline can be performed as correlative work. For patients, reaching CR/sCR MRD negative timepoint earlier where MRD negative status is confirmed at earlier bone marrow evaluation, bone marrow aspiration and biopsy at end of study will be optional. Otherwise, all other bone marrow biopsies are mandatory.
i. After study therapy ends, follow-up will be 1 month after study end date. Patients may be followed at more frequent time intervals, and thereafter if clinically indicated. Patients who have progressive disease while on therapy will be followed with restaging scans and labor atory tests as clinically indicated. At disease progression, marrow and FDG-PET/CT are optional but recommended.
j. For patients with intial baseline 24-hr UPEP samples demonstrating ≥100 mg/24 hrs, patients with continue to have 24-hr UPEP samples day 1 of each cycle. Once 24-hr UPEP is <100 mg/24 hrs, patient can have random UPEP with IFE until achieving negativit y. If initial baseline 24-hr UPEP sample is IFE positive and/or <100 mg/24, patients can have random UPEP samples with IFE until achieving negativity. On ce random UPEP and IFE is negative, no further urine samples are needed (unless patient's disease is primarily measurable by 24 hr urines)

k. FDG-PET scan will be performed on patients at baseline, end of therapy or upon suspicion of progressive disease as clinically indicated. End of therapy FDG-PET scan can be performed +/- 21 days.
l. Treatment window for day 1 of start of each cycle is +/- 7 days. Treatment window for intra-cycle carfilzomib doses is + 2 days. .
m. After 1- and 3-year from completing therapy, PFS and OS data will be collected on patients. Patients will option of having formal evaluation with H&P, clinical labs, myeloma labs and bone marrow evaluating for MRD status. PFS and OS data may be collected over the phone along with review of medical records. Survival, PFS, and time to next line of treatment data may be collected on subsequent protocols that patients have consented for (maintenance protocols/bio-banking or storage protocols).
n. Patients will have an EKG and echocardiogram (2-D or strain) performed at baseline and after completion of 4 cycles of therapy. Outside echocardiograms are permissible

Clinical and Correlative Studies - To create a bone marrow (clinical pathology, whole BM lysate, CD 138+ fractions and CD 138- fractions cell sorting with subsequent correlatives on both fractions), peripheral blood, and urine sample bank. These samples may be used to later to evaluate biological activity of carfilzomib, lenalidomide, and dexamethasone. Timepoints and potential analyses are listed below:

Bone Marrow

Sampling Time Points of Bone Marrow correlative studies

a) Baseline
b) CR/sCR during cycles 2-and up to 12
c) End of therapy
d) 1 and 3 year timepoints after completing therapy (optional)

	Baseline	**During Cycles 2-12 if reaches CR/sCR**	**End of study therapy**	**1 and 3 year timepoints after completing therapy**
Pathology/IHC	x	x	x	x
Multiparametric Flow Cytometry	x	X*	X*	x
FISH/Cytogenetics	x			
Molecular Pathology for light or heavy chain immunoglobulin rearrangement	x	x	x	x
Storage (sorted and whole cell lysate)	x	X	X	X

*Patients undergoing MRD evaluation or End of study evaluation, the first pulled sample will be sent for Multiparametric flow cytometry. For those patients that are MRD negative by flow cytometry during their routine pre-stem cell collection bone marrow assessments, the result will count towards their MRD evaluation.

- Potential studies on the stored bone marrow samples may include but are not limited to the following:

Bone Marrow Aspirate/Biopsy

Pathology/Immunohistochemistry

Immunohistochemical staining will be assessed using immunohistochemistry markers such as CD 138, light chains, CD56 etc. Microenvironment interactions will also be assessed using various immunohistochemistry markers for osteoblasts, osteoclasts, stromal cells and proteasome components.

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 (CD38 bright and/or CD138 positive) include but are not limited to decreased or absent CD19 and CD45, decreased CD38, increased CD56, decreased CD27, decreased CD81, increased CD117. For patients with non-evaluable samples at MRD assessment, patients can opt for repeat MRD assessment or continue to receive a total of 8 cycles of CRd. For those patients that are MRD negative by flow cytometry during their routine pre-stem cell collection bone marrow assessments, the result will count towards their MRD evaluation. The first pulled bone marrow sample will be sent for multi-parametric flow cytometry as a priority. Samples will undergo MRD testing per MSK institutional practice, see section 12.0 for further methodology practice.

Molecular pathology: For MRD samples utilizing the NGS LymphoSIGHT™ (Sequenta, Inc., South San Francisco, CA) platform, immunoglobulin heavy and kappa chain variable, diversity, and joining gene segments from genomic DNA obtained from CD138+ bone marrow (BM) cell lysate or cell-free supernatant BM aspirate were amplified using universal primer sets as described elsewhere[21]. An MM clonotype was defined as an immunoglobulin rearrangement identified by NGS at a frequency of ≥5%.

Mass spectrometry based proteomics for minimal residual disease assessment: Serial urine and serum samples will be analyzed to detect clonotypic peptides representing patient's monoclonal immunoglobulin heavy and light chains using high resolution mass-spectrometry-based proteomics.

FISH and cytogenetics

Interphase FISH/cytogenetics will be performed on patients enrolled in this protocol.

DNA-based target mutations

Bone marrow aspirate samples will be analyzed for somatic mutations by exome-sequencing of targeted genes using FoundationOne Heme platform (or equivalent i.e. MSK Impact Heme). After therapy, perform if response is ≤PR or evidence of gross residual disease on SPEP/UPEP

Cell Sorting and Bone marrow cell lysate

Bone marrow aspirate storage samples will be sorted into CD 138 + and CD 138 – fractions and whole bone marrow cell lysate per HOTB SOP.

Research Blood/Serum and Urine

a) One 7-8 mL serum tube will be collected at baseline, Day 2, Day 8, Day 15, and Day 22 of Cycle 1, Day 1 of every cycle during cycles 2-up to 12, during Cycles 2-12 if **CR/sCR** is achieved, at the end of therapy, and at any time point if the patient has progression of disease. One 7-8 mL EDTA tube will be collected at baseline Day 1 of every cycle during cycles 2-up to 12, during Cycles 2-12 if **CR/sCR** is achieved, at the end of therapy, and at any time point if the patient has progression of disease.
b) Urine (random samples of 10 mL) will be collected into a standard urine collection cup and sent for analysis and storage at each of the above timepoints. Time points include: baseline, Day 2, Day 8, Day 15 and Day 22 of Cycle 1, Day 1 of every cycle during cycles 2-up to 12, during Cycles 2- up to 12 if **CR/sCR** is achieved, at the end of therapy, , and at any time point

if the patient has progression of disease.

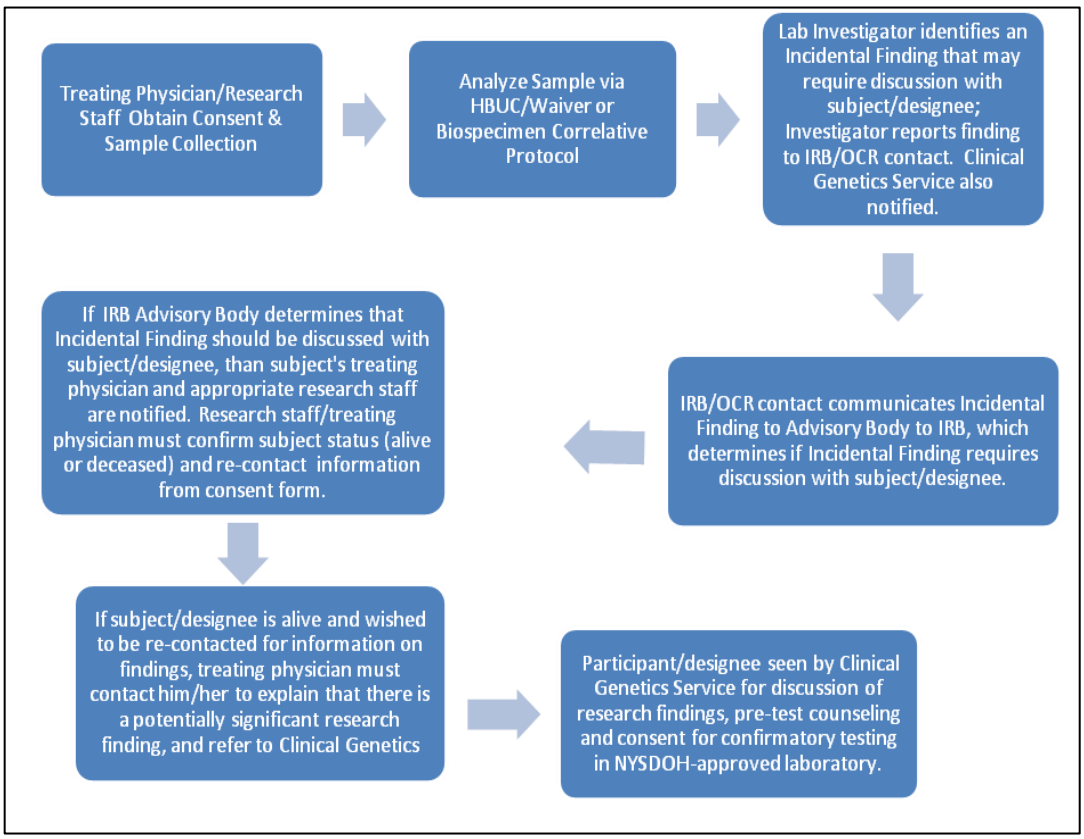
c) Peripheral blood and/or urine samples from patients will be analyzed for potential serum or urine biomarkers as well as drug concentrations, and describe the association with clinical outcomes if the results of the study indicate a clinical or translational rationale for analyzing the samples.

Assessment/Evaluation Plan

The protocol consent form asks participants for permission for re-contact to discuss research findings if an incidental research finding is made that may be critical to their health or preventive care, or that of their issue. If a participant agrees to be re-contacted, he/she will not be told the specific results of the research test, but will be informed that his/her samples were used in a project and a potential risk was discovered. If the participant is interested in further discussion of the research findings, he/she will be asked to contact MSKCC Clinical Genetics Service for counseling and specific genetic testing.

The below schema will be followed by MSKCC investigators who identify a potentially actionable incidental finding in the course of research conducted on samples collected under this protocol:

In the event an investigator's research identifies a finding that he or she believes should be communicated to the subject (and/or family designee), the investigator shall communicate this to the OCR-IRB. The finding will be reviewed by a group convened by the IRB to determine whether the incidental finding should be discussed with the subject. In the event that group determines that the finding should be discussed with the subject, and the subject has consented to be re-contacted, then the treating/consenting physician shall be contacted by the OCR-IRB representative and asked to refer the subject to the Clinical Genetics Service for further discussion of the research finding. After appropriate counseling and consent, the Clinical Genetics Service will request permission to confirm the result in a New York DOH-approved laboratory prior to communication of the specific result. If the patient is not available (e.g. deceased), then the surrogate designated on the consent will be contacted and the above will occur.



The IRB and Clinical Genetics Service, as per above flow chart, will be notified when a participant's samples uncover a potentially reportable incidental finding(s). The following information must be provided to OCR-IRB representative and Clinical Genetics:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, etc)
- Incidental Finding
- Project # (Waiver or Biospecimen Protocol #) that this analysis occurred under
- Collection Protocol #

Contact: ocrgapirb@mskcc.org

11.0 TOXICITIES/SIDE EFFECTS

11.1 Carfilzomib

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

- Fatigue (tiredness)
- Fever
- Headache
- Cough

- Shortness of breath (at rest or with exertion) which in rare cases may be life-threatening or resulting in death
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Decreased red blood cell count which may lead to feeling tired
- Decreased platelet counts which may lead to increase bleeding or bruising
- Decreased white blood cell count which may decrease your ability to fight infection
- Upper respiratory tract infection
- Mild decreases in kidney function which are generally reversible
- Swelling of the arms or legs
- Back pain
- Inflammation of the liver (mild, reversible changes in liver function tests)

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

- 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
- Decreased or worsening of heart function including chest pain, abnormal heart rhythm, heart attack, and heart failure. This can be serious, potentially life threatening event.
- Loss of or decreased appetite which may lead to weight loss
- Insomnia (difficulty sleeping)
- Dizziness
- High blood pressure
- Abnormal physical weakness or lack of energy
- Blurred or double vision
- Numbness, tingling, painful or decreased sensation in hands and/or feet
- Blood chemistry and electrolyte alterations
- Rash and/or itching, or dry skin
- Pneumonia
- Pain, burning, or irritation at the infusion site
- Generalized pain
- Pain in the bones or joint pain or extremities
- Muscle spasm, pain, or weakness

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:

- Herpes zoster reactivation
- Liver failure
- Acute kidney failure
- Increase in the blood pressure in the arteries of the lungs (Pulmonary Hypertension)
- Infusion reactions (which can occur during or shortly after carfilzomib infusion) including flushing or feeling hot, fever, shakes, nausea, vomiting, weakness, shortness of breath, swelling of the face, pain in the muscles or joints, tightness or pain in the chest, and low blood pressure
- Allergic reaction including total blood rash, hives, and difficulty breathing
- Tumor Lysis Syndrome: Caused by rapid killing of tumor cells during dosing. When the tumor cells die, they release their contents into the bloodstream. If cell killing is very rapid, this can affect

blood chemistries and the kidneys. In severe cases, this can lead to shutdown of kidney function requiring dialysis

- Posterior reversible encephalopathy syndrome (PRES): A rare condition that causes swelling of the brain and affects how it functions. A person with PRES may experience headaches, confusion, loss or decreased level of consciousness, blurred vision or blindness, seizures, and possibly death. If caught early and treated, PRES may be reversed.

11.2 Lenalidomide

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

- Low number of white blood cells (with or without fever)
- Anemia (lowered red blood cells)
- Decrease in cells that help your blood clot (lowered platelets)
- Swelling in legs and/or extremities
- Diarrhea
- Constipation
- Nausea
- Feeling weak and unwell, fatigue
- Fever
- Chills
- Rash
- Pain including muscles, joints, back, and non-cardiac chest pain
- Dizziness
- Shaking or tremor
- Shortness of breath
- Upper respiratory tract infection

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

- Vision Blurred
- Altered sense of taste
- Pain or decreased sensation of touch
- Pneumonia
- Urinary tract infection
- Increased sweating
- Dry skin
- Itching
- Decreased appetite
- Weight loss
- Vomiting
- Abdominal pain
- Dry mouth
- Electrolyte imbalance in blood
- Blood clot in lower or upper extremities
- Lowered level of consciousness with drowsiness, listlessness, and apathy

- Abnormal liver lab tests
- Loss of fluid
- Muscle weakness
- Tingling of skin
- High or low blood pressure

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 lenalidomide:

- Lowered white blood cells with fever
- Blood clot to lung
- Irregular heart beat
- Congestive heart failure – abnormal functioning of heart leading to fluid in lungs and extremities
- Stroke
- Immune destruction of red blood cells (autoimmune hemolytic anemia)
- Slow heart rate or fast heart rate
- Heart attack
- Blindness
- Mood swings, hallucinations
- Gastrointestinal bleed
- Severe skin allergic reactions: lining of the nose, mouth, stomach and intestines or rash leading to the separation of the top layer of skin, swelling under the skin
- Rapid death of cancer cells where the accumulating contents of dying cancer cells cause an imbalance in the chemistry of the body which can lead to kidney damage.
- Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing baby.
- Second primary cancers

11.3 Dexamethasone

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

- Increase in appetite
- Weight gain
- Fatigue
- Fluid retention, which can lead to swelling in the legs, arms and within the face
- High blood pressure
- Rise in the blood sugar
- Problems with low levels of potassium in the blood
- Menstrual cycle disturbances
- Depression or Mood swings or changes in personality
- Trouble with sleeping
- Dizziness
- Headache
- Slow wound healing
- Thin, fragile skin, black and blue marks
- Increased sweating and/or flushing
- Increase in body hair
- Bone thinning, which can lead to spinal fracture or destruction or fracture of the long bones (thigh/hip and upper arm/shoulder)
- Hormonal disturbances during times of stress or illness
- Hiccups
- Nausea
  Rash – mild acne
- Increased risk of infections. This can be a serious, potentially life threatening event.
- Yeast infections

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

- Stomach ulcers or worsening or irritation or existing ulcers. This can be serious, potentially life threatening event.
- Muscle weakness or loss of muscle mass
- Inflammation of the pancreas
- Cataract formation
- Glaucoma
- Rupture of tendons
- Vein blood clots in the veins of the legs or lungs. This can be a serious potentially life threatening event.

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 lenalidomide:

- Severe allergic reactions (including facial redness, shortness of breath, profuse perspiration, abdominal cramps, fast heart beat, and low blood pressure - severe allergic reactions).
- Brain swelling.
- Convulsions.
- Formation of a hole in the small and/or large bowel particularly in people with preexisting bowel problems. This can be a serious, potentially life threatening event.
- Irritation and bleeding of the esophagus (the tube from the mouth of the stomach)
- If you are more prone to heart disease, you may experience heart failure
- Aseptic necrosis (bone death) of the hip

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Disease Parameters

a) A "measurable" serum M-protein is ≥ 1 g/dL or a "measurable" urine M-spike is ≥ 200 mg/24 hours or “measurable light chains” are 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.

b) The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have light-chain 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 if the baseline level of the involved FLC is ≥10mg/dL and abnormal kappa/lambda ratio (when primary determinant of response).

c) For patients with intial baseline 24-hr UPEP samples demonstrating ≥100 mg/24 hrs, patients with continue to have 24-hr UPEP samples day 1 of each cycle. Once 24-hr UPEP is <100 mg/24 hrs, patient can have random UPEP with IFE until achieving negativity. If initial baseline 24-hr UPEP sample is IFE positive and/or <100 mg/24, patients can have random UPEP samples with IFE until achieving negativity. Once random UPEP and IFE is negative, no further urine samples are needed (unless primary determinant of response)

d) In order to be classified as a 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 at different timepoints.

e) Compression fracture does not exclude continued response and may not indicate progression; findings of worsening compression fracture will be subject to interpretation of the clinical investigator.

Minimal Residual Disease

For patients undergoing MRD or end of study assessment, the first pulled bone marrow sample will be sent for multi-parametric flow cytometry as a priority. Flow cytometry based assay to rule out MRD (defined as less than 20 abnormal plasma cells) in bone marrow aspirates of CR/sCR patients. For patients with samples demonstrating between 10-20 abnormal plasma cells, cases will be reviewed with hematopathologist and clinical investigator on a case by case basis to determine whether sample is considered MRD positive. Patients with <CR/sCR are considered MRD positive. We will use the MSKCC flow cytometry MRD method which is based on 10-colors in a single tube.[16]. The test demonstrates highly similar results when compared to the current Euroflow approach. This test is validated and already in clinical use at MSK. 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 (CD38 bright and/or CD138 positive) include but are not limited to decreased or absent CD19 and CD45, decreased CD38, increased CD56, decreased CD27, decreased CD81, increased CD117. For patients with non-evaluable samples at MRD assessment, patients can opt for repeat MRD assessment or continue to receive a total of 12 cycles of CRd. For those patients that are MRD negative by flow cytometry during their routine pre-stem cell collection bone marrow assessments,

the result will count towards their MRD evaluation.

Traditional Response Criteria from International Myeloma Working Group Criteria for Multiple Myeloma[22]

Evaluation of Response Criteria

a) 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.

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

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

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

e) 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.

f) Progressive disease (PD)
   - Requires any one or more of the following:
     - Increase of ≥ 25% of nadir in:
     - Serum M-component and/or (absolute increase must be ≥ 0.5 g/dl. The serum M-component increases of ≥ 1gm/dl are sufficient to define relapse if starting M-component is ≥ 5 gm/dl.
     - Urine M-component and/or (the absolute increase must be ≥ 200 mg/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

g) Relapse from CR
   - Any one or more of the following:
     - Reappearance of serum or urine M-protein by immunofixation or electrophoresis. (Appearance of monoclonal or oligoclonal bands that are different from original isotype may not be defined as "relapse from CR". Often times, such bands may indicate fluctuations in immunological parameters that are not reflective of MM disease. In these situations, immunofixation and electrophoresis will be interpreted by the clinican before being labeled as "relapse"[23,24].
     - Development of ≥ 5% plasma cells in the bone marrow
     - Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, hypercalcemia

Progression-Free Survival

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

Overall Survival

Overall survival is defined as the time of start of treatment to death from any cause.

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).

13.0 CRITERIA FOR REMOVAL FROM STUDY

Off-therapy Criteria

Patients with medically concerning grade 3 or 4 adverse events related to drug therapy may be taken off therapy at the discretion of the principal investigator.

- Patients who require more than 2 dose reductions of carfilzomib
- Hematologic toxicity has not completely resolved or resolved to < grade 1 or baseline after 2 weeks of withholding treatment
- Therapy has been held for more than 3 weeks due to treating a grade 3 infection
- Grade 4 non-blistering rash or blistering rash of any grade
- Grade 4 neuropathy
- Grade 4 hypersensitivity reaction
- Patient experiencing significant cardiac event as outlined in section 9.5

- Patient completes the protocol treatment
- Progression of disease
- Patient chooses to go off therapy
- The principal investigator may remove patient from protocol therapy if deemed necessary due to medical conditions, compliance, etc.
- Patient becomes pregnant.

Off-Study Criteria

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

  Patient has completed 1- and 3-year evaluation from end of therapy

14.0 BIOSTATISTICS

Phase I:

The goal of the phase I trial is to find the maximum tolerated dose (MTD) of carfilzomib when used in combination with lenalidomide and dexamethason. The trial design is a standard 3 by 3 dose escalation design. The three carfilzomib dose levels that will be explored are listed in Section 4.2.2 and the DLT evaluation window is the first cycle of therapy. The DLT definition is provided in Section 4.2.1.

1. A cohort of three patients will be enrolled at the first dose level (45/mg/m^2). If no DLTs are observed in the cohort, the next dose level will be explored.
2. If one DLT is observed in the initial cohort of three, an additional three patients will be treated at the same dose level. If no additional patients have a DLT, the next dose level will be explored.
3. If at any point two or more patients have a DLT at a given dose level, the MTD will have been exceeded and the previous dose level will need to be investigated.
4. If three patients are treated at a potential MTD, the dose cohort will be expanded to six for confirmation.

Using this dose escalation scheme, escalation to the next treatment level is probable if the risk of DLT is low, and the likelihood of escalations decreases as the risk of DLT increases, as demonstrated in table below:

Table Dose Escalation/Toxicity Risk

True risk of Toxicity	.10	.20	.30	.40	.50	.60
Probability of Escalation	.91	.71	.49	.31	.17	.08

The minimum and maximum sample size for the phase I trial is 4 and 18, respectively. It is anticipated that 1-2 patients per month may enroll on this trial; thus, approximately one year or less is anticipated as the accrual period for the phase I study.

Phase II:

The phase II component of this trial will explore the efficacy of the combination therapy using the carfilzomib dose selected in the phase I trial. The primary endpoint is CR/sCR MRD negativity (MRD-) rate by flow cytometry upon or prior to completion of 12 cycles of therapy. Patients with <CR/sCR are considered MRD positive. Based on previous research an CR/sCR MRD- rate by flow cytometry of 45% would be promising enough to warrant further investigation, while a rate of 20% would not be promising for further investigation. Using a Simon's optimal two-stage design, the first stage of the trial will enroll 14 patients. This includes the three-six patients treated at the MTD in the phase I trial. If three patients or fewer are CR/sCR MRD- by flow cytometry, the trial will stop due to a lack of efficacy; otherwise, an additional 11 will enroll to a total sample size of 25 at end of phase II. If at least eight patients are MRD- (at the MTD), the intervention will be considered promising for further research. The type 1 error is set at 0.10 and the type II error is set at 0.10. If the true MRD- rate is 20%, the probability of early termination is 70%. For patients that come off trial prior to completion of 4 cycles of therapy, due to reasons unrelated to disease progression or toxicities, patients can be replaced (max 3) for MRD evaluation as part of the phase II assessment.

It is anticipated that 1-2 patients per month may enroll on this trial; thus, approximately one year is anticipated as the accrual period for the phase II study. The total maximum possible projected sample size for the study is 37 patients.

Secondary endpoints for both Phase I and II:

1. To estimate the overall response rate (ORR) according to International Myeloma Working Group criteria at each cycle and as the best response during the treatment of up to 12 cycles. In addition to ORR, the rates of VGPR+CR and CR alone will also be estimated and reported. The exact 95% confidence intervals will also be included.
2. Kaplan-Meier methodology will be used to estimate progression-free survival and overall survival . Estimates of survival along be with 95% confidence intervals will be provided for select time points.
3. To explore the concordance of different MRD methodologies. MRD status by multiparametric flow cytometry will be compared to next-generation sequencing and to mass spectrometry based proteomics methodologies. The concordance across the different technologies will be reported along with an exact 95% confidence interval.
4. To create a bone marrow and peripheral blood sample bank. These samples may be used to later evaluate the biological activity of carfilzomib, lenalidomide, and dexamethasone. Potential analyses include sequencing and gene expression profiling on pre and post therapy bone marrow samples, identification of potential biomarkers (blood, urine, bone marrow aspirates), and evaluation of proteasome activity.

Exploratory Studies:

1. The gene panel HemePACT (or alternative equivalent platform) will explore whether any mutations appear to be associated with response to therapy or toxicity associated with therapy. This descriptive aim will combine patients across all dose levels. This analysis is for hypothesis-generation, and all results will be cautiously interpreted. Fisher's exact test

may be used to assess any potential association. The variant allele frequency (VAF) will be summarized for each mutation.

2. HemePACT (or alternative equivalent platform) will also be evaluated using samples at the time of progression of disease or during an ongoing response and will be compared to the pre-treatment baseline samples to explore whether pathways leading to emergence of resistance to the drug regimen can be identified. Similar to the previous objective, this aim is for hypothesis generation, and all results will be cautiously interpreted. Changes in the VAF from baseline will be summarized for patients with an ongoing response and for patients who have progression of disease. A paired t-test may be used to further describe this association. This aim will combine patients across all explored dose levels.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

This study will not include randomization.

16.0 DATA MANAGEMENT ISSUES

All patients will be enrolled on protocol at Memorial Sloan-Kettering Cancer Center. We expect to be able to enroll the necessary 34 patients into this study in 2 years.

The data manager (Clinical Research Coordinator/CRC) will be responsible for confirming eligibility and assisting the MD with the registration process. All study data will be collected by an assigned CRC who will enter this information into the Clinical Research Database (CRDB). This database will be utilized for data collection and storage and for reporting protocol specific events such as accrual demographics, toxicities and adverse events to the IRB, and the sponsor.

The CRC will collect toxicity and concomitant medication information and patient interviews. Adverse events, including all toxic effects of treatment will be tabulated individually according to severity or toxicity grade. The data manager will also monitor laboratory testing throughout

the study. Laboratory data will be tabulated and summarized by descriptive statistics, as well as on the basis of MSKCC specified normal ranges.

16.1 Quality Assurance

Monthly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC and collaborating centers IRB guidelines.

Patients will be eligible for this trial regardless of gender or racial/ethnic background. All patients must follow the guidelines for pregnancy testing birth control and counseling related to the risk of fetal exposure to lenalidomide and bortezomib.

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent also indicates that samples and genetic information collected may be shared with other qualified researchers. Such information will not include identifying information such as name. It is also stated in the consent and Research Authorization that research data (e.g. genomic sequence) may be placed into databases monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government.

Consent for re-contact

Patients are asked in a series of check boxes at the end of the consent if 1) if they consent to be contacted to discuss research findings which may derive from their sample; and 2) if not available (e.g. deceased), if they wish to have their designated representative on the consent to be contacted.

Use of identifiable information for genetic studies

It will be explained to participants that future research may also be done to identify changes in genes that predict risk for cancer or other diseases; if such germline genetic research is perfomed, then to be in compliance with New York State law (see section 3.5), it will not be possible to provide results of research tests not performed in a New York State Department of Health approved clinical laboratory. It is stated in the consent that participants will be told that they will not receive any specific results from potential research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSKCC Clinical Genetics Service.

If in the course of this research a research finding is obtained that may be critical to the preventive care of the participant or their family, as determined by procedures overseen by the IRB, those participants, if they consent to checklist questions 1, 2, will be referred to the Clinical Genetics Service for a consulation. At that time, genetic counseling can be offered in accordance with New York State requirements, and appropriate clinical testing offered in an

approved laboratory. Please see flow chart and requirements for reporting under section 10.0.

Patients will be informed that future research may also identify changes in genes that predict risks for cancer or other diseases. Procedures for informing patients or their designees, confirmation by a New York State approved laboratory, and followup assessments and counseling are already detailed in Section 10.0 above.

For tumor (somatic) genetic studies, germline studies of genetic variants of unknown significance (e.g. for example, in pharmacogenetics studies), gene discovery studies, and cellular, immunologic, or other studies using banked correlative tissues, the name and personal identifiers may be removed from the sample, but a coded link will be maintained.

Research analysis of tumor genomes may inadvertently reveal, or require some knowledge of the germline genome. Such research studies could be performed on samples not identifiable to the researcher but with identifying links maintained by the TPS, HOTB or similar, and approved via IRB mechanisms. See section 10.0 for instructions on how to report incidental findings on research samples.

Future use of samples

Researchers at MSKCC may either keep indefinitely or dispose of any specimen(s) collected under this protocol including DNA that the samples contain. Specimens will be stored with identifiers in secure banks. Samples could be lost or ruined because of mechanical failure, and MSKCC cannot guarantee that samples will be stored indefinitely. The samples will be stored for as long as deemed useful for research purposes.

Risks of research participation

Risks are those of the procedure to obtain the specimen and are considered minimal. Another risk is release of information from health or research records in a way that violates privacy rights. MSKCC protects records so that name, address, phone number, and any other information that identifies the participant will be kept private and confidential, along with all personal health information.

Benefits of research participation

It is unlikely that the research using biospecimens will be of any medical benefit to participants. Neither the patient nor the treating physician will necessarily be told of the results of any research tests on the samples, except an incidental finding that may be critical to the preventive care of the subject or his/her issue. Research using biospecimens collected in this study could lead to medical and scientific products that could improve prevention, diagnosis, and treatment of disease; but those benefits are unlikely to accrue to the participants.

Occasionally, however, there are tests conducted in research labs, the results of which might contribute toward treatment decisions. These studies would not yet have been reduced to clinical practice, but patients may be informed of such results and how they may affect diagnosis and treatment.

Costs/compensation

There is no cost to enroll or participate in this research. Biospecimens obtained under this research protocol may be used to make secondary products, and such products may be patented or licensed with commercial value. Participants are not financially compensated for use of their human biological specimens or secondary products, tests, and discoveries that derive from their biospecimens.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient of participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/ intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test of procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the adverse event was expected
- Detailed text that includes the following
    - An explanation of how the adverse event was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

17.2.1

SAE Reporting by Investigator-sponsor to Amgen

The Investigator-sponsor must be notified of the occurrence of any SAE within 24 hours of the investigator, designee, or site personnel's knowledge of the event. The Investigator-sponsor is responsible for notifying the appropriate health authorities (HAs), ethics committees (ECs), and investigators, of any expedited, annual, or other periodic safety reports in accordance with applicable regulations. Any safety report submission will cross reference the Amgen investigational new drug (IND) or clinical trial approval (CTA) number.

The Investigator is also responsible for notifying the local ECs in accordance with local regulations.

The Investigator-sponsor must inform Amgen in writing by e-mail or fax at the contact information listed below for all SUSARs that are judged as reasonably related to the Amgen study drug. Site will transmit the final CIOMS of that event to Amgen within twenty-four (24) hours of submitting the report to the applicable regulatory authority.

For regulatory reporting purposes, an event of "Death, Cause Unknown" from the study shall be processed as a SUSAR. All forms must be completed and provided to Amgen in English.

The Individual Case Safety Report (ICSR) may be referred to as an individual safety report or SAE Report, including Pregnancy Exposure Reports and Follow up Reports. The ICSR must be as complete as possible, at a minimum including event reference number, protocol name and number, investigator contact information, specific patient identifiers (e.g., initials, patient number, date of birth or age, or gender), the name of the suspect Study Drug, the date and dosage(s) of exposure, event, the date(s) of event, country of event, "Serious" Criteria, Relationship/causality of Study Drug, Hospitalization history for the event, Event status/outcome, Relevant history (including diagnostics, laboratory values, radiographs, concomitant medications, and event treatment, and narrative summary.

Sponsor shall be responsible for collecting all SAEs and Pregnancy and Lactation Exposure Reports and will exercise commercially reasonable due diligence to obtain follow-up information on incomplete SAE or Pregnancy and Lactation Exposure Reports. In the event that the Company requires clarification or further information on individual SAE or Pregnancy and Lactation Exposure Reports, Company will not contact non-party investigators directly, but will route all such inquiries through Site for forwarding to such investigator(s). Site will be responsible to ensure such inquiries are completed and timely provided to Company.

Information not available at the time of the initial report (e.g., an end date for the SAE, discharge summaries, lot numbers, relevant laboratory values, scan data and autopsy reports) which are received after the initial report must be documented on a follow-up form, and submitted to Amgen in the same timelines as outlined above. Sponsor shall be responsible for obtaining follow-up information for the SAEs and demonstrate diligence in attempting to obtain such information by, among other things, maintaining written records of such attempts.

Other aggregate analysis including reports containing safety data generated during the course of the study is to be submitted to Amgen at the time the sponsor ISS submits to anybody governing research conduct i.e. RA, IRB etc. Final study report including unblinding data when applicable and reports of unauthorized use of a marketed product to be submitted to Amgen at the time the sponsor ISS submits to anybody governing research conduct i.e. RA, IRB etc. but not later than one calendar year of study completion.

Sponsor will provide an annual IND report to Amgen. Reports containing safety data generated during the course of the study is to be submitted to Amgen at the time the sponsor submits to anybody governing research conduct, i.e. regulatory authorities and IRBs. Sponsor will support reconciliation of all ICSRs at the end of the study at a minimum.

Reporting Pregnancy to Amgen

Pregnancy Reporting by Investigator-sponsor to Amgen

Report Pregnancy and potential infant exposure including Lactation, within ten (10) calendar days of Sponsor awareness. Provide to Amgen the SAE reports associated with pregnancy. SUSARs are to be reported within twenty-four (24) hours of submitting the report to the applicable regulatory authority.

Amgen Global Safety Contact Information

- Toll-free #:1-888-814-8653
- For countries where the U.S. toll-free # cannot be used: +44-20-7136-1046
- Email (Only for sponsors with a secure email connection with Amgen): svc-ags-in-us@amgen.com

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 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
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.comdrugsafety@celgene.com

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

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Appendix A: Requirements for REMS®

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

Requirements for REMS®

- Patients should be instructed never to give lenalidomide to another person.
- Patients will be asked to take part in a mandatory confidential survey prior to initiation of lenalidomide. To take the survey, they will be instructed to call the 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. Monthly phone counseling is required per the REMS® program in order to prescribe a one-month supply of lenalidomide.
- All patients will be required to sign the REVLIMID, Patient-Physician Agreement Form.
- Males must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy. See below for further details
- Females of childbearing potential must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation. See below for further details.

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

Risks Associated with Pregnancy

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

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

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal

for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

The investigator must ensure that:

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

Contraception

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

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

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

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

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

Pregnancy testing

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

Before starting lenalidomide

Female Patients:

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

Male Patients:

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

<u>During study participation and for 28 days following lenalidomide discontinuation</u>

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.

<u>Male Patients:</u>

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

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

APPENDIX B

To characterize bone marrow aspirate specimens for somatic base mutations and copy number alterations in key cancer-associated genes, we will perform a custom, targeted deep-sequencing assay on matched tumor and normal pairs. The assay, termed HEMEPACT

involves massively parallel sequencing, coupled with solution-phase exon capture. Exon capture will be performed on barcoded pools of sequence libraries by hybridization (Nimblegen SeqCap Target Enrichment) using custom oligonucleotides to capture all exons and select introns of 585 cancer genes, including all genes significantly mutated in hematologic malignancies. Barcoded pools will subsequently be sequenced on an Illumina HiSeq 2500 to 500-1000x coverage per sample in order to maximize sensitivity for detecting low-abundance alterations. Through many iterations of the design of the capture probe set, we have maximized the coverage uniformity across all exons in our panel, thus reducing the number of poorly-covered exons. As a result, for a sample sequenced by HEMEPACT to 1000x coverage, >98% of target exons are covered at >500x. The platform includes all genes that are druggable by approved therapies or are targets of experimental therapies being investigated in clinical trials at MSKCC. Custom probes have been designed to capture translocations involving recurrently rearranged genes.