*MSK PROTOCOL COVER SHEET*

# Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone in Newly-Diagnosed Multiple Myeloma: A Clinical and Correlative Phase II Study

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## 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase II study to assess the safety and efficacy of 8 cycles of combinational therapy with DARZALEX™ (daratumumab), carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma (MM) patients.

Primary Objective:

The primary objective of the study is to assess the rate of MRD negativity after completion of the combination therapy using multiparametric flow cytometry

Secondary Objectives:

1. To determine safety and tolerability.
2. 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.
3. To estimate overall survival (OS) and progression-free survival(PFS).
4. To compare MRD techniques of multi-parametric flow cytometry with next-generation sequencing and mass spectrometry.
5. To create a bone marrow, urine, stool, and peripheral blood sample bank. These samples may be used to later-evaluate biological activity of daratumumab, 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, stool, bone marrow aspirates) associated with clinical outcomes.

Exploratory Objectives:

1. The gene panel myTYPE will explore whether any mutations appear to be associated with response to therapy or toxicity.

2. myTYPE will 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.
3. To evaluate the effects on stem cell mobilization quality in patients receiving daratumamab, carfilzomib, lenalidomide, and dexamethasone. Examples of data being collected but not limited to will include the following: number of patients undergoing stem cell mobilization, demographics, cycles received prior to stem cell mobilization, CD34 blood counts prior to collection, total stem cell yield, mobilization failure rates, and subsequent attempts of mobilization.

Patient Population

Newly diagnosed patients with histologically confirmed multiple myeloma.

Study Design

- Two-cohort, two-stage phase II trial of combination therapy (daratumumab, carfilzomib, lenalidomide, and dexamethasone [DKRd]) for newly diagnosed multiple myeloma patients
- Each cycle consists of 28 days
- After 4-6 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 8 cycles of induction combination therapy of DKRd. Patients will undergo evaluation for response at monthly intervals using IMW uniform response criteria (Kumar. et al. Lancet Oncol 2016) 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 study treatment at completion of 4 cycles.
- Patients achieving >PR at end of 4 cycles, will continue to receive the planned total of 8 cycles of combination therapy
    - Patients obtaining CR/sCR at any point during cycles 1-8 in serum and urine will undergo MRD testing using multi-parametric flow cytometry.
- Upon completion of protocol therapy, eligible 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, including annual MRD assessment when appropriate.

Treatment Plan (see schema below)

Cohort 1:

- Cycle 1 ONLY: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 20 mg/m$^2$ per dose, days 2 and 3; Carfilzomib 36 mg/m$^2$ per dose, days 8, 9, 15, and 16; Dexamethasone 20 mg/dose, days 1,2, 3, 8, 9, 15, 16, and 22 ; Lenalidomide 25 mg/day, days 2–21 every 28 days; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg. Montelukast 10 mg will be administered prior to the first 4 doses of Daratumumab.
- Cycle 2: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.

- Cycles 3-6: Daratumumab 16 mg/kg days 1 and 15; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 7-8: Daratumumab 16 mg/kg day 1; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 2-8: Carfilzomib 36 mg/m$^2$ per dose, days 1, 2, 8, 9, 15, and 16
- Cycles 2-8: Lenalidomide 25 mg/day, days 1-21 every 28 days
- Cycles 2: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15, 16, and 22
- Cycles 3-4: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15, and 16
- Cycles 5- 8: Dexamethasone 10 mg/dose, days 1, 2, 8, 9, 15, and 16

- After receiving 4 or more cycles, patients who are considered to be eligible for subsequent high dose therapy/autologous stem cell transplant (ASCT) will be recommended to undergo autologous stem cell harvesting for potential use in the future. For patients who choose to undergo stem cell harvest, the subsequent cycle may be delayed for up to 7 weeks.

Cohort 2:

- Cycle 1 ONLY: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 20 mg/m$^2$ per dose, day 2; Carfilzomib 56 mg/m$^2$ per dose, days 8 and 15; Dexamethasone 20 mg/dose, days 1,2, and 22, 40mg/dose days 8 and 15; Lenalidomide 25 mg/day, days 2–21 every 28 days; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg. Montelukast 10 mg will be administered prior to the first 4 doses of Daratumumab.
- Cycle 2: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
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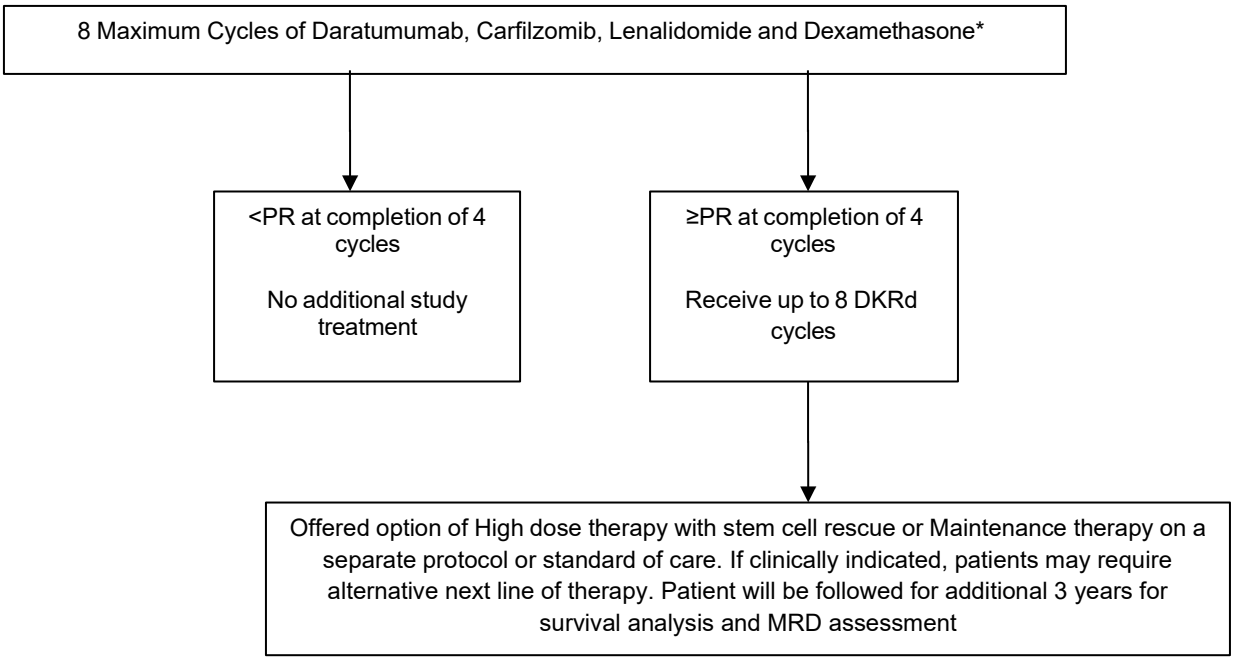
**Cohorts 1 and 2:**

- Patients achieving ≥PR at end of 4 cycles will continue to receive the planned total of 8 cycles of combination therapy. Patients may go onto receiving additional maintenance phase therapy with lenalidomide under a separate treatment protocol.
- Patients <PR after completing 4 cycles will go off study therapy.
- Upon completion of protocol therapy, eligible 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, including annual MRD assessment when appropriate.

## 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.

* The two cohorts will differ based on the frequency and dose level of Carfilzomib taken per cycle.

## 2.0 OBJECTIVES AND SCIENTIFIC AIMS

This is a phase II study to assess the safety and efficacy of 8 cycles of combinational therapy with DARZALEX™ (daratumumab), carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma MM patients.

Primary Objective:

The primary objective of the study is to assess the rate of MRD negativity after completion of the combination therapy using multiparametric flow cytometry.

Secondary Objectives:

1. To determine safety and tolerability.
2. 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.
3. To estimate overall and progression-free survival.
4. To compare MRD techniques of multi-parametric flow cytometry with next-generation sequencing and mass spectrometry.
5. To create a bone marrow ,urine, and peripheral blood sample bank. These samples may be used to later evaluate biological activity of daratumumab, 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) associated with clinical outcomes.

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1. The gene panel myTYPE will explore whether any mutations appear to be associated with response to therapy or toxicity.

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# 3.0 BACKGROUND AND RATIONALE

## Introduction

Multiple Myeloma and Carfilzomib

Multiple myeloma is characterized by clonal proliferation of malignant plasma cells in the bone marrow, affecting an estimated 25,000 people in the US annually [1]; about 100,000 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 6-7 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 (KRd)[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 KRd in patients with newly diagnosed MM patients[12],[1]. 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 KRd, 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 $\geq$ 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[14]. The KRd 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). In that study, using next generation sequencing molecular tests the CR/sCR MRD negative rate was 13/33 (39%) [12,13].

DARZALEX™ (daratumumab)

CD38 is a 45-kD, type II transmembrane glycoprotein that associates with cell-surface receptors in lipid rafts, regulates cytoplasmic $Ca^{2+}$ flux, and mediates signal transduction in lymphoid and myeloid cells[15,16]. CD38 is highly and uniformly expressed on myeloma cells[17,18] and is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of nonhematopoietic origin, which makes it a potential target in the treatment of myeloma[16]. Daratumumab (HuMax-CD38, Genmab), a human IgG1κ monoclonal antibody, binds to a unique CD38 epitope [19]. Preclinical studies showed that daratumumab induced target-cell killing of CD38-expressing tumor cells by means of multiple mechanisms, including complement-mediated and antibody-dependent cell-mediated cytotoxic effects, antibody-dependent cellular phagocytosis, apoptosis[19], and to a lesser extent, inhibition of the enzymatic activity of CD38. Early phase clinical trials have established the single agent activity and efficacy of this drug in patients with relapsed and/or refractory myeloma patients [20]. Furthermore, the drug is fairly well tolerated with infusion related reactions being the most common adverse events [20].

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). 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[22]. 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 in the 10-color 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 . 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 cytometry platform against next generation sequencing and mass spectrometry. These studies will help us to better understand and further develop details of various MRD methods.

Daratumumab in Combination with Carfilzomib, Dexamethasone and Lenalidomide

The results of the interim analysis show 11 participants have reached MRD negativity with an average of 5.36 cycles in Cohort 1 while 10 participants have reached MRD negativity with an average of 4.5 cycles in Cohort 2. There are 2 participants and 18 participants pending a best MRD response within 8 cycles of combination therapy for Cohort 1 and 2, respectively. As of May 2019, Cohort 2 has shown a 100% MRD negativity rate as a best response within 8 cycles of combination therapy. Cohort 2 is based on weekly dosing schedule that reduces the number of visits by 50% from Cohort 1 with Carfilzomib 56 mg/m2 per dose.

Randomization Cohort Treatment Arms

Randomization allows objectivity for assigning treatment arms. Attal et al. published results that showed participants treated with RVD induction therapy achieved MRD negativity at 65%. However, overall survival at 4 years between the transplantation group and the RVD only alone group was similar (81% and 82%, respectively)[47]. In a later study, Perrot et al. showed 25% MRD negativity was achieved at least once during maintenance with in 127 patients who were treated with RVD induction therapy alone[48].

Evidence supports KRd induction is favorable induction therapy for NDMM and SMM as one study has shown 28 patients with NDMM and the 12 with SMM achieved a-near CR with 28 of 28 found to be MRD negative from the JAMA Oncology paper on the NCI KRd phase 2 study (Korde et al, 2015)[49].

## 3.2 Proposed Study Investigation with Correlative Studies

Given the potent anti-myeloma activity of the KRd 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 have developed this phase II investigation in newly diagnosed MM employing carfilzomib at 20/36 mg/m$^2$ and 20/56 mg/m$^2$ with lenalidomide and dexamethasone in combination with daratumumab, administered over 8 twenty-eight day cycles.

After 4 or more cycles of treatment with DKRd, 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 DKRd. M-spikes and FLCs will be monitored every month. Patients achieving <PR after completion of 4 cycles of therapy will stop protocol therapy. Patients who are ≥ PR after 4 completed cycles will receive additional 4 (i.e. a total of 8) cycles of DKRd. At any point during protocol, if patients achieve CR/sCR by serum and/or urine assessments[25], patients will undergo bone marrow examination to confirm CR per standard criteria: a minimum of a bone marrow aspirate must be collected, however a biopsy can also be performed per institutional practice. The first pulled bone marrow sample will be sent for multi-parametric flow cytometry as a priority sample. Upon completion of protocol therapy, eligible 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 daratumumab, carfilzomib, lenalidomide, and dexamethasone.

The study is designed to estimate the rate MRD for daratumumab in combination with carfilzomib and lenalidomide/dexamethasone **and** further describe the safety profile of the combination. Our study is novel since no prior myeloma study has been designed to use MRD as the primary endpoint in newly diagnosed multiple myeloma. 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 II study and treated with 4-drug combination of daratumumab, carfilzomib, lenalidomide, and dexamethasone. New data demonstrates that 56mg/$m^2$ has the same safety profile as 36mg/$m^2$ in the newly diagnosed multiple myeloma patients treated with the 3-drug combo KRd[26]. Efficacy for Carfilzomib has a dose-response association and emerging data indicates that once a week 56mg/$m^2$ and twice a week 36mg/$m^2$ translates into similar CR rates. To make the 4 drug combinations more convenient to patients, the study has expanded to include two parallel cohorts; one cohort with twice a week 36mg/$m^2$ and the other cohort with once a week 56mg/$m^2$ Carfilzomib, respectively. Up to 82 patients will be enrolled on study; 41 patients per cohort. Clinical response as well as MRD rates will be determined the same way in both cohorts. The overall goal is to develop a highly efficacious combination, and to optimize the dosing so it becomes as convenient as possible. The combination of efficacy and convenience is of direct benefit to patients.

### 4.2 Intervention

Cohort 1:

- Cycle 1 ONLY: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 20 mg/$m^2$ per dose, days 2 and 3; Carfilzomib 36 mg/$m^2$ per dose, days 8, 9, 15,

and 16; Dexamethasone 20 mg/dose, days 1, 2, 3, 8, 9, 15, 16 and 22 ; Lenalidomide 25 mg/day, days 2 – 21 every 28 days; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg. Montelukast 10 mg will be administered prior to the first 4 doses of Daratumumab

- Cycle 2: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 3-6: Daratumumab 16 mg/kg days 1 and 15; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
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- Cycles 5- 8: Dexamethasone 10 mg/dose, days 1, 2, 8, 9, 15 and 16

Cohort 2:

- Cycle 1 ONLY: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 20 mg/m$^2$ per dose, day 2; Carfilzomib 56 mg/m$^2$ per dose, days 8 and 15; Dexamethasone 20 mg/dose, days 1,2, and 22, 40mg/dose days 8 and 15; Lenalidomide 25 mg/day, days 2–21 every 28 days; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg. Montelukast 10 mg will be administered prior to the first 4 doses of Daratumumab.
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Cohorts 1 and 2:

- After receiving 4 or more cycles, patients who are considered to be eligible for subsequent high dose therapy/autologous stem cell transplant (ASCT) will be recommended to 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.
- Patients achieving ≥PR at end of 4 cycles will continue to receive the planned total of 8 cycles of combination therapy. Patients may go onto receiving additional maintenance phase therapy with lenalidomide under a separate treatment protocol.
- Patients <PR after completing 4 cycles will go off study therapy.
- Upon completion of protocol therapy, eligible 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, including annual MRD assessment when appropriate.

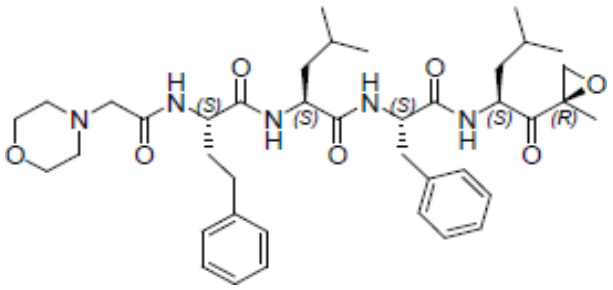
## 5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

## Carfilzomib

### 5.1.1 Scientific Background

Carfilzomib is a tetrapeptide ketoepoxide-based irreversible inhibitor developed by AMGEN 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 supply will be obtained through commercial supply for cohort 1. Carfilzomib will be supplied by Amgen for cohort 2. Carfilzomib for Injection is provided as a lyophilized powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®). Lyophilized Carfilzomib for Injection is stored in a refrigerator at 2°C–8°C. Water for injection is the only acceptable solution for reconstitution. After addition of the appropriate amount of water for injection and vigorous mixing, the solution is administered as an IV infusion. Vials are for single use. Carfilzomib will be prepared and administered as per MSKCC or local Guidelines.

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 Onyx 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.
- Onyx 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 30-minutes 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:

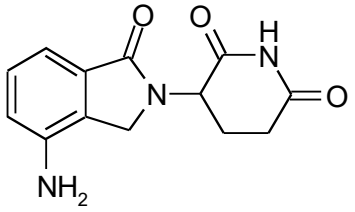
In an in vitro study using human liver microsomes, carfilzomib showed modest direct and time-dependent inhibitory effect on human cytochrome CYP3A4/5. Given that the clearance of carfilzomib likely occurs extrahepatically via the activity of epoxide hydrolase and peptidase activities, the clinical relevance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

Lenalidomide supply will be obtained through commercial supply. Lenalidomide will be supplied as capsules for oral administration (capsules are 5, 10, 15 and 25 mg).

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:

.The cost of Revlimid® (lenalidomide) will be paid for by the patient and/or the patient's health plan/insurance company. 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

Lenalidomide related diarrhea

This study will evaluate the symptom burden of lenalidomide-related diarrhea and the potential role of the gut microbiota in the pathoetiology of lenalidomide-related diarrhea. Continuous lenalidomide treatment until relapse or disease progression has led to significant improvements in overall survival and progression-free survival[54-59].However, continuous lenalidomide use can lead to development of diarrhea in up to 40% of patients. Chronic diarrhea can significantly affect quality of life in an older population with a high incidence of neuropathy and can lead to premature discontinuation of therapy. A recent report linked lenalidomide related diarrhea to bile acid malabsorption and intestinal

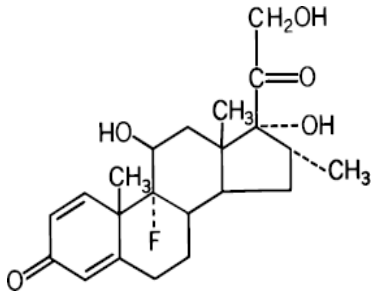
bacterial overgrowth[60]. The gut microbiota are essential to normal bile acid metabolism and alterations in gut flora that lead to bile acid diarrhea are well-described[61-63]. The effects of lenalidomide use on microbiota and the etiology of lenalidomide related diarrhea remain unknown. We aim to gather information about changes in the gut microbiota to explore if lenalidomide use leads to diarrhea in association with alterations in the gut microbiota. Stool will be collected at baseline prior to starting therapy, at time of CR or disease progression, and at study completion. Stool samples should also be collected close to time of onset of reported symptoms of diarrhea or at the investigator's discretion. To obtain food and beverage consumption, a validated Block Questionnaire (Food and Activity Questionnaire) will be administered to patients once.

## 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 can be given orally or IV.

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

### 5.4 Daratumumab

DARZALEX™ (daratumumab) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, in a variety of hematological malignancies including MM, leukemia, and non-Hodgkin's lymphoma (NHL).

Daratumumab induces lysis of CD38-expressing tumor cells, by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), through activation of complement proteins, natural killer (NK) cells, and macrophages, respectively [de Weers 2011, Overdijk 2013][2,20]. For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding daratumumab, refer to the latest version of the Investigator's Brochure [Daratumumab IB].

Preliminary pharmacodynamic studies suggest that daratumumab utilizes multiple effector cell functions, resulting in immune mediated killing of CD38-expressing tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary CD38-expressing MM cells, complement-dependent cytotoxicity (CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody- mediated activation of the complement proteins (de Weers 2011)[2]. Daratumumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC) is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro (de Weers 2011)[2]. Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro (Overdijk 2013)[20]. Further, in vitro studies indicated that daratumumab inhibited the cyclase activity of CD38 and stimulated the CD38 hydrolase activity (Study No. GMB 3003-013).

Studies on proliferation of and release of cytokines in human blood cells have indicated that daratumumab does not exert target-specific agonistic activity. The cytokine release observed is mainly caused by the Fc-portion of IgG1 and comparable to that of approved therapeutic antibodies already in clinical use. Specific binding of daratumumab was detected in multiple tissues of both human and chimpanzee origin.

In general, daratumumab is tolerated well. Maximum tolerated dose (MTD) has not been reached following intravenous (IV) infusions up to 24 mg/kg monotherapy and 16 mg/kg in combination studies. The most frequently reported adverse events (AEs) across the daratumumab program have been infusion-related reactions (IRRs) following single agent therapy. Among all subjects treated in ongoing studies (monotherapy and combination therapy), IRRs have been reported in 49% of subjects; among 151 subjects treated with 16 mg/kg daratumumab monotherapy in Studies GEN501 and MMY2002, the percentage of subjects with a reported IRR was identical (49%) to what was observed across all treated subjects. The most frequently reported AEs (reported in ≥5% of subjects) reported as IRRs were rhinitis allergic (8%), cough (7%), and nasal congestion (6%). Among subjects treated with 16 mg/kg daratumumab monotherapy, the most commonly reported IRRs were nasal congestion (8%), cough (7%), and rhinitis allergic and throat irritation (5% each). Grade 3 or higher IRRs were reported in 5% of subjects treated with 16 mg/kg daratumumab as monotherapy, with bronchospasm and hypertension being the most frequently reported Grade 3 or higher IRRs (1% each).

Across all ongoing studies, bronchospasm was reported in 10 subjects. Early in daratumumab development, in Study GEN501, 2 cases of bronchospasm were reported 24-48 hours following the second full-dose infusion of daratumumab. With the exception of those 2 cases, which had a delayed onset, all other reported bronchospasm events occurred following the first dose. All of the events occurring during the infusion period resolved quickly after standard treatments were administered. The daratumumab infusion was restarted, and no new onset of bronchospasm occurred. Most of the subjects who experienced bronchospasm had underlying respiratory diseases (asthma, chronic obstructive pulmonary disease [COPD], and others).

Daratumumab was FDA approved for the indication of relapsed myeloma in November 2015. The initial approval was single drug used for 3rd line therapy. In October of 2016 FDA label was updated to include daratumumab with Revlimid/dexamethasone as 2nd line therapy; also the updated FDA label include daratumumab with Velcade/dexamethasone as 2nd line therapy. In June 2017, the FDA label was updated again; daratumumab with Pomalidomide/dexamethasone as 2nd line therapy. There is an ongoing randomized phase 3 study investigating daratumumab with Revlimid/dexamethasone as front line therapy. The drug combination we are testing (carfilzomib, daratumumab with Revlimid/dexamethasone) has been assessed in a phase 1 study which was recently presented at ASCO in June 2017.25 In the phase 1 trial the dosing of carfilzomib was 70 mg/m2 once a week; we are planning on giving 36 mg/m2 twice a week in cohort 1 since that is the NCCN approved dose and 56mg/m2 once a week in cohort 2. ***Daratumumab rate of infusion is per MSKCC guidelines.***

Among the 151 subjects treated with 16 mg/kg daratumumab as monotherapy in Studies GEN501 and MMY2002, the most frequently reported AEs (reported in >10% of subjects) were fatigue (29%); anemia (23%); nausea (19%); back pain (18%); cough (17%); thrombocytopenia (16%); decreased appetite (13%); pyrexia, dyspnea, upper respiratory tract infection (12% each); nasal congestion and neutropenia (11% each). Grade 3 and higher AEs were reported in 48% of subjects treated with 16 mg/kg monotherapy daratumumab. The most frequently reported Grade 3 or higher AEs were anemia (13%) and thrombocytopenia (9%). All other Grade 3 and higher

AEs were reported in <5% of subjects. No deaths due to daratumumab-related AEs have been reported in any ongoing study.

# 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, MDRD, or CKD-EPI formulae

- 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 2weeks 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 2 weeks from last dose (on a trial or outside a trial) are eligible

- Plasma cell leukemia
- POEMS syndrome
- Amyloidosis

- Has known chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal (note that FEV1 testing is required for subjects suspected of having chronic obstructive pulmonary disease and subjects must be excluded if FEV1 <50% of predicted normal).

- Pregnant or lactating females. Because 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

- Subject is:

    - Seropositive for human immunodeficiency virus (HIV)

    - Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.*

    - Seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

- 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.

- Pulmonary hypertension

- 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. All patients will be seen by a myeloma physician and associated study co-investigator, 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 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 (HBsAg)
  - Hepatitis B surface antibody (Anti-HBs)
  - Hepatitis B core antibody (Anti-HBc)
  - Anti-Hepatitis C (HCV) antibody. If positive, will follow with HCV RNA PCR
  - HIV antibodies 1 & 2
- Review of bone marrow core biopsy and aspirate.
- Serum or urine pregnancy test in women of child-bearing potential.
- 12-lead EKG
- Echocardiogram
- Daratumumab Type and Screen Immunotherapy
- Stool sample collection

HBV Serology

Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment 7 is implemented will be required to have HBV serology performed locally upon signing the updated ICF.

HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose.

HBV DNA Tests:

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Time and Events Schedule (Section 10.0). Where required by local law, the results of HBV testing may be reported to the local health authorities.

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.
    - Sample for NGS MRD should be bone marrow aspirate (not biopsy and not CD138 purified, per the assay validation) 1mL, frozen at -70$^{o}$C.
    - Patients who have completed 1 cycle of SOC therapy who meet eligibility criteria and have an HOTB sample at MSK within 60 days of cycle 1 day 1, will not need an additional bone marrow biopsy or aspirate, unless clinically indicated.
- 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.
    - Indirect Coombs Test or other tests required by the local blood bank needed before treatment with CD38-antibodies.

<u>Imaging (FDG/PET/CT scan) within 8 weeks of study entry and prior to starting therapy</u>

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]-fludeoxyglucose 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 8 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. Patients who have completed 1 cycle of SOC therapy who meet eligibility criteria and have had a PET scan read at MSK within 60 days of cycle 1 day 1, will not need an additional PET scan, unless clinically indicated

## 9.0 TREATMENT/INTERVENTION PLAN

Patients who have signed the consent form and are deemed eligible for this clinical trial will start therapy 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 and/or daratumumab doses is +/- 2 days.
- These cycles will consist of:

**Cohort 1**

- Cycle 1 ONLY: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 20 mg/m$^2$ per dose, days 2 and 3; Carfilzomib 36 mg/m$^2$ per dose, days 8, 9, 15, and 16; Dexamethasone 20 mg/dose, days 1, 2, 3 , 8, 9, 15, 16 and 22; Lenalidomide 25 mg/day, days 2 – 21 every 28 days; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg. Montelukast 10 mg will be administered prior to the first 4 doses of Daratumumab.
- Cycle 2: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 3-6: Daratumumab 16 mg/kg days 1 and 15; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 7-8: Daratumumab 16 mg/kg day 1; Acetaminophen 650 mg ; intravenous Diphenhydramine 25 mg.
- Cycles 2-8: Carfilzomib 36 mg/m$^2$ per dose, days 1, 2, 8, 9, 15, and 16
- Cycles 2-8: Lenalidomide 25 mg/day, days 1-21 every 28 days
- Cycles 2: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15, 16 and 22
- Cycles 3-4: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15 and 16
- Cycles 5- 8: Dexamethasone 10 mg/dose, days 1, 2, 8, 9, 15 and 16

**Cohort 2**

- Cycle 1 ONLY: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 20 mg/m$^2$ per dose, day 2; Carfilzomib 56 mg/m$^2$ per dose, days 8 and 15; Dexamethasone 20 mg/dose, days 1,2, and 22, 40 mg/dose days 8 and 15 ; Lenalidomide 25 mg/day, days 2–21 every 28 days; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg. Montelukast 10 mg will be administered prior to the first 4 doses of Daratumumab.
- Cycle 2: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.

- Cycles 3-6: Daratumumab 16 mg/kg days 1 and 15; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 7-8: Daratumumab 16 mg/kg day 1; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 2-8: Carfilzomib 56 mg/$m^2$ per dose, days 1, 8, and 15
- Cycles 2-8: Lenalidomide 25 mg/day, days 1-21 every 28 days
- Cycles 2: Dexamethasone 40 mg/dose, days 1, 8, and 15; 20 mg/dose day 22
- Cycles 3-4: Dexamethasone 40mg/dose, Days 1, 8 15
- Cycles 5-8: Dexamethasone 20mg/dose, Days 1, 8, 15

- After receiving 4 or more cycles, patients who are considered to be eligible for subsequent high dose therapy/autologous stem cell transplant (ASCT) will be recommended to undergo autologous stem cell harvesting for potential use in the future. For patients who choose to undergo stem cell harvest, the subsequent cycle may be delayed for up to 7 weeks.

**Cohorts 1,and 2**

- Patients achieving ≥PR at end of 4 cycles will continue to receive the planned total of 8 cycles of combination therapy.
- Patients <PR after completing 4 cycles will go off study therapy.
- After completion of protocol therapy, patients will remain on study for an additional 3 years for survival analysis, including annual MRD assessment when appropriate.

Daratumumab was FDA approved for the indication of relapsed myeloma in November 2015. The initial approval was single drug used for 3rd line therapy. In October of 2016 FDA label was updated to include daratumumab with Revlimid/dexamethasone as 2nd line therapy; also the updated FDA label include daratumumab with Velcade/dexamethasone as 2nd line therapy. In June 2017, the FDA label was updated again; daratumumab with Pomalidomide/dexamethasone as 2nd line therapy. There is an ongoing randomized phase 3 study investigating daratumumab with Revlimid/dexamethasone as front line therapy. The drug combination we are testing (carfilzomib, daratumumab with Revlimid/dexamethasone) has been assessed in a phase 1 study which was recently presented at ASCO in June 2017.[25] In the phase 1 trial the dosing of carfilzomib was 70 mg/m2 once a week; we are planning on giving 36 mg/m2 twice a week in cohort 1 since that is the NCCN approved dose and 56mg/m2 once a week in cohort 2.

## 9.1 Dose Modifications

Dose reductions are not permissible for daratumumab. Below are dose reductions for the other drugs used on this protocol.

### 9.1.1 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 |

### 9.1.2 Dose Reductions for Carfilzomib

| | Carfilzomib |
|---|---|
| Baseline dose | 36 mg/m$^2$ |
| One level dose reduction | 27 mg/m$^2$ |
| Two level dose reduction | 20 mg/m$^2$ |

| | Carfilzomib |
|---|---|
| Baseline dose | 56 mg/m$^2$ |

| | Carfilzomib |
|---|---|
| One level dose reduction | 45 mg/m$^2$ |
| Two level dose reduction | 36 mg/m$^2$ |
| Three level dose reduction | 27 mg/m$^2$ |
| Four level dose reduction | 20 mg/m$^2$ |

### 9.1.3 Dose Reductions for Dexamethasone

| | Dexamethasone |
|---|---|
| Baseline dose | 20 mg |
| One level dose reduction | 10 mg |
| Two level dose reduction | 4 mg |
| Three level dose reduction | 0 mg |

** Note: Dexamethasone dose may be further reduced at investigator's discretion**

| | Dexamethasone |
|---|---|
| Baseline dose | 40mg |
| One level dose reduction | 20mg |

| | |
|---|---|
| Two level dose reduction | 5 mg |
| Three level dose reduction | 0 mg |

** Note: Dexamethasone dose may be further reduced at investigator's discretion**

### 9.1.4 Infusion Related Reaction (IRR) Management - Daratumumab

Severe infusion reactions associated with Daratumumab include bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension . Patients will be pre-medicated with antihistamines, antipyretics and corticosteroids and frequently monitored during entire infusion. Infusions will be interrupted for interactions of any severity and medical management will be managed. Daratumumab will be permanently discontinued for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, the infusion rate will be reduced when re-starting the infusion.

To reduce the risk of delayed infusion reactions, corticosteroids will be given to all patients.)]. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. In these instances post-infusion short and long-acting bronchodilators, and inhaled corticosteroids medications maybe perscribed. If the patient experiences no major infusion reactions, following the first four infusions, these additional inhaled post-infusion medications may be discontinued.

## 9.2. Hematologic Toxicity

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

- ANC ≥ 1.0 x $10^9$ /L
- Platelet count ≥ 50 x $10^9$ /L

9.2.2 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.
- 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.

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

| **Thrombocytopenia** | **Lenalidomide** | **Carfilzomib** |
|---|---|---|
| Fall to < 25 x $10^9$/L | Hold both Lenalidomide and Carfilzomib, follow CBC 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.

## 9.3 Non-Hematologic Toxicities Requiring Dosing Modifications

9.3.1 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.

9.3.2 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.

9.3.3 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 be attributed to study drugs. If the adverse event was deemed to be unrelated to study drugs, the patient may continue the full dose.

9.3.4 Electrolyte or metabolic abnormalities that are reversible with electrolyte replacement within 48 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<br><br>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<br>• CrCl ≤30 mL/min (not requiring dialysis) – Dose reduce Lenalidomide to 15 mg every 48 hours<br>• 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.<br><br>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 | Patients with clinical symptoms and/or significant changes in EF (>10%) will hold carfilzomib and repeat cardioechogram as clinically appropriate; if persisting/worsening clinical symptoms and/or significant changes in EF that is attributed to the therapy, the patient will be taken off the trial. |
| 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.<br><br>Hypertension emergency – stop therapy and go off protocol |
| Myocardial infarction | Any patient experiencing myocardial infarction will stop therapy and go off protocol |
| Posterior reversible encephalopathy syndrome (PRES) | If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If the diagnosis of PRES is excluded, carfilzomib administration may resume at the same dose, if clinically appropriate. |

| Carfilzomib Toxicities | Specific Dosing Modifications |
|---|---|
| Thombotic microangiopathy (TMA) | If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA is confirmed, permanently discontinue carfilzomib. If the diagnosis is excluded, carfilzomib can be restarted. |
| Hepatitis B reactivation | Carriers of HBV who require treatment with Kyprolis should be closely monitored for signs and symptoms of active HBV infection throughout treatment. Any subject who becomes HBV DNA positive or develops reactivation of HBV should have carfilzomib treatment interrupted and receive appropriate anti-viral treatment as per a specialist in Hepatitis B. |
| Progressive Multifocal Leukoencephalopathy | Patients should be monitored for any new or worsening neurologic, cognitive or behavioral signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders.<br>If PML is suspected, patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue Kyprolis if PML disagnosis is confirmed. |

## 9.4 Monitoring

9.4.1 Routine labs (CBC, chemistry panel 14, LDH, magnesium, uric acid, phosphate) will be performed at baseline and on Day 1, 2, 8, 15, and 22 of cycle 1 and 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 and 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.

9.4.2 For patients with initial 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)

9.4.3 Patients will have clinic visits with H&P or standard progress notes assessing for toxicity/side effects on Day 1, 8, and 15, of cycle 1 and Day 1 of each cycle thereafter 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 +/- 2 days. Vital signs will be checked prior to administration of study drugs carfilzomib or daratumumab in all cycles.

9.4.4 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 biopsy 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 laboratories and H&P) 1 month after completing combination therapy to undergo assessment of toxicities/adverse events.

9.4.5 Patients will have an echocardiogram (2-D or strain echo) performed at baseline and after completion of 6 cycles of therapy. Outside echocardiograms are permissible.

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

9.4.7 PFS and OS data will be collected for patients.

9.4.8 Stool sample collections are mandatory Stool samples will be collected prior to start of treatment during screening or before starting cycle 1, after cycle 1 (+14 days), and End of Protocol Therapy (EOS) +/- 14 days.

9.4.9 A medication log will be provided to patients to capture antibiotic use for patients collecting stool samples. Antibiotic use is not prohibited, but data will be captured for correlative purposes relating to analysis of stool microbiota.

### 9.5 After Protocol Therapy

9.5.1 Upon completion of protocol therapy, eligible 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.

9.5.2 After completion of protocol therapy, patients will remain on study for an additional 3 years for survival analysis, including annual MRD assessment when appropriate.

## 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.

### Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation see Section 10.0.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

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

**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. The investigators do not anticipate the need for using rasburicase but it should be used if necessary according to indication and local guidelines.

## 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) Bisphosphonate therapy: Approved bisphosphonate 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.
4) Denusumab: Approved denosumab treatment is allowed.

## HYPERCALCEMIA

Patients may receive treatment for hypercalcemia including hydration, bisphosphonates, 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 darbepoetin.
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, or similar anti-emetics on day 1, 8, and 15 can be administered at the discretion of the treating physician.

## 10.0 EVALUATION DURING TREATMENT/INTERVENTION

| Study | Pre-Treatment | Induction | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycle 1[l] | | | | | | | | Cycles 2-8 | | | End of Therapy | 1 month after EOT [i,l] | 1, 2, and 3 years after EOT [i,m] |
| | | Day 1 | Day 2 | Day 8 | Day 9 | Day 15 | Day 16 | Day 22 | Day 23 | Day 1[lO] | After completing 4-8 cycles | CR/sCR reached | | | |
| Medical Record Review | x | | | | | | | | | | | | x | x | x |
| H&P with blood pressure | x | x | | x | | x | | | | x | | | x | x | x[m] |
| Echo + EKG | x | | | | | | | | | | x[n] | | | | |
| ECOG | x | | | | | | | | | x | | | x | | |
| Informed Consent | x | | | | | | | | | | | | | | |
| Viral Studies[b] | x | | | | | | | | | x[b] | | | x[b] | x[b] | x[b] |
| Register for RevAssist | x | | | | | | | | | | | | | | |
| Routine Labs[a] | x | x | x | x | | x | | x | | x | x[a] | | 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 | | |
| **Daratumumab Type and Screen Immunotherapy** | x | | | | | | | | | | | | | | |
| **Stool Sample collection** | X[o] | | | | | | | | | X[o] | | | X[o] | | |
| **Adverse Events/Toxicity** | | x | | | | | | | | x | | | x | x | |
| **Daratumumab[p]** | | x | | x | | x | | x | | X[p] | | | | | |
| **Carfilzomib[p]** | | x | x | x | x | x | x | | | X[p] | | | | | |
| **Lenalidomide[p]** | | | x | x | x | x | x | x | x | X[p] | | | | | |
| **Dexamethasone[p]** | | x | x | x | x | x | x | x | | X[p] | | | | | |
| **Acetaminophen/[p] Diphenhydramine** | | x | | x | | x | | x | | X[p] | | | | | |
| **Montelukast [p]** | | 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. PT and PTT will only be performed at baseline. Peripheral blood lymphocyte subsets at baseline, C4D1, and end of therapy. Complete Blood Count (CBC) WITH Differential will be performed on days 8 and 15 during cycles 2-8.

b. Viral studies include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) and Hep C antibody. If Hep C antibody positive, Hep C RNA PCR will be performed.

- *HPV DNA testing (if applicable)*: For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Treatment Phase: Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment. Refer to Section 8.0.

c. Pregnancy tests (urine or serum) for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months)

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

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

g. Bone marrow aspiration and biopsy will be sent for histopathology, flow cytometry, FISH/cytogenetics, heavy/light chain immunoglobulin 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. Patients who have completed 1 cycle of standard of care therapy who meet eligibility criteria and have an HOTB sample at MSK within 60 days of cycle 1 day 1, will not need an additional bone marrow biopsy or aspirate, unless clinically indicated.

h. Bone marrow aspirate and biopsy can be performed +/- 21 days of intended cycle day or achievement of CR/sCR. Bone marrow aspirate and biopsy will be sent to evaluate for histopathology, flow cytometry (bone marrow immunophenotyping of plasma cells), heavy/light chain immunoglobulin 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. 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 as per standard of care. Otherwise, all other bone marrow biopsies are strongly encourage for all cohorts.
i. After study therapy ends at the completion of 8 cycles or after 4 cycles in patients who have <PR, 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 laboratory tests as clinically indicated. At disease progression, marrow and FDG-PET/CT are optional but recommended.
j. For patients with initial baseline 24-hr UPEP samples demonstrating ≥100 mg/24 hrs, patients will 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)
k. FDG-PET scan will be performed on patients at baseline, end of therapy or upon suspicion of progressive disease as clinically indicated..
l. Variations of +/- 7 days of scheduled visits are permitted (Treatment window for day 1 of start of each cycle is +/- 7 days. Treatment window for intra-cycle carfilzomib and/or daratumumab doses is +/- 2 days). Patients who have completed 1 cycle of standard of care therapy who meet eligibility criteria and have had a PET scan read at MSK within 60 days of cycle 1 day 1, will not need an additional PET scan read at MSK within 60 days of cycle 1 day 1, unless clinically indicated.
m. After 1, 2 and 3-year from completing therapy (+/- 1 month window), PFS and OS data will be collected on all patients. Patients will have formal evaluation with H&P, clinical labs, myeloma labs and bone marrow evaluating for MRD status as per standard of care. 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 echocardiogram (2-D or strain) performed at baseline and after completion of 6 cycles of therapy. Outside echocardiograms are permissible
o. Stool samples will be collected prior to start of treatment during screening or before starting cycle 1, after cycle 1 (+14 day permitted) and End of Study (EOS) +/-14 days A food frequency questionnaire will be administered to patients once either on study or in follow up.
p. The treatment schedule for cycles 1-8 is as follows:
   *Cohort 1:*
   - Cycle 1 ONLY: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 20 mg/m$^2$ per dose, days 2 and 3; Carfilzomib 36 mg/m$^2$ per dose, days 8, 9, 15, and 16; Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15, 16 and 22; Lenalidomide 25 mg/day, days 2 – 21 every 28 days; Montelukast 10 mg (first 4 doses of Daratumumab)
   - Cycle 2: Daratumumab 16 mg/kg days 1, 8, 15, and 22
   - Cycles 3-6: Daratumumab 16 mg/kg days 1 and 15

- Cycles 7-8: Daratumumab 16 mg/kg day 1
- Cycles 2-8: Carfilzomib 36 mg/m$^2$ per dose, days 1, 2, 8, 9, 15, and 16
- Cycles 2-8: Lenalidomide 25 mg/day, days 1-21 every 28 days
- Cycles 2: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15, 16 and 22
- Cycles 3-4: Dexamethasone 20 mg/dose, days 1, 2, 8, 9, 15 and 16
- Cycles 5- 8: Dexamethasone 10 mg/dose, days 1, 2, 8, 9, 15 and 16

*Cohort 2:*

- Cycle 1 ONLY: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Carfilzomib 20 mg/m$^2$ per dose, day 2; Carfilzomib 56 mg/m$^2$ per dose, days 8 and 15; Dexamethasone 20 mg/dose, days 1,2, and 22, 40 mg/dose days 8 and 15; Lenalidomide 25 mg/day, days 2–21 every 28 days; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg. Montelukast 10 mg will be administered prior to the first 4 doses of Daratumumab.
- Cycle 2: Daratumumab 16 mg/kg days 1, 8, 15, and 22; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 3-6: Daratumumab 16 mg/kg days 1 and 15; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 7-8: Daratumumab 16 mg/kg day 1; Acetaminophen 650 mg; intravenous Diphenhydramine 25 mg.
- Cycles 2-8: Carfilzomib 56 mg/m$^2$ per dose, days 1, 8, and 15
- Cycles 2-8: Lenalidomide 25 mg/day, days 1-21 every 28 days
- Cycles 2: Dexamethasone 40 mg/dose, days 1, 8, and 15; 20 mg/dose day 22
- Cycles 3-4: Dexamethasone 40mg/dose, Days 1, 8 15
- Cycles 5-8: Dexamethasone 20mg/dose, Days 1, 8, 15
- After receiving 4 or more cycles, patients who are considered to be eligible for subsequent high dose therapy/autologous stem cell transplant (ASCT) will be recommended to undergo autologous stem cell harvesting for potential use in the future. For patients who choose to undergo stem cell harvest, the subsequent cycle may be delayed for up to 7 weeks.

**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 daratumumab, 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 8
c) End of therapy
d) 1, 2 and 3 year timepoints after completing therapy (optional)

| | **Baseline** | **During Cycles 2-8 if reaches CR/sCR** | **End of study therapy** | **1,2, 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

- 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. 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™ (Adaptive, CA) platform, the InVivoScript NGS 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.

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 MSK *myTYPE* platform (or equivalent e.g. 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 8, during Cycles 2-8 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 CPT tube will be collected at baseline Day 1 of every cycle during cycles 2-8, 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 2-8, 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.

Stool

a) Stool samples will be collected at baseline or prior to start of cycle 1, after cycle 1 end of cycle 8 or end of study. Stool should also be collected at time of complete response and at time of disease progression. Sample may also be collected at investigator's discretion at a time point that corresponds to onset of reported symptoms.
b) Volume: 2-5 mL of stool should be collected using the provided stool collection kit.
c) Sample requirements and handling: Date and approximate time of stool collection should be noted and logged with the requisition form and on the personalized label on the stool container. Stool should be collected within up to 24 hours of sample submission using instructions provided to patient, and kept refrigerated using cold packs provided with sample collection kit provided to patient, until sample can be delivered to the processing laboratory/delivery location denoted on the requisition form.

Stem cell mobilizaton

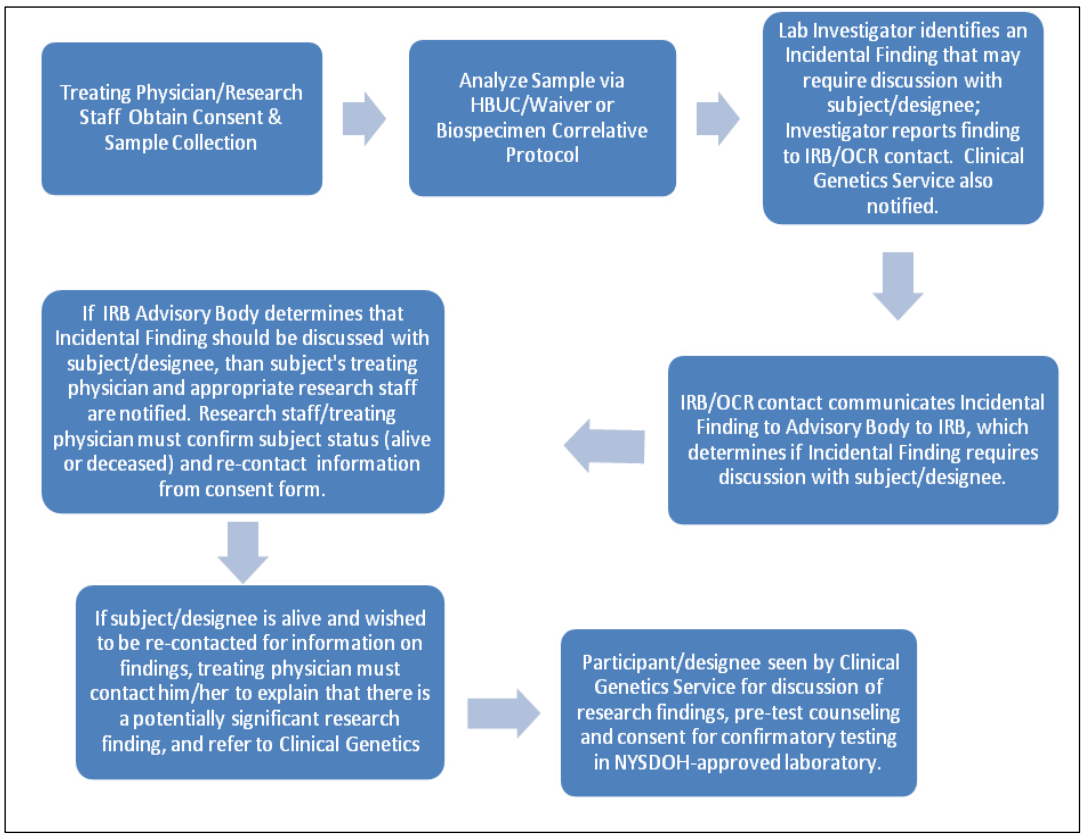
a) Clinical de-identified data will be collected on the quality of stem cell mobilization. Examples of data being collected but not limited to will include the following: number of patients undergoing stem cell mobilization, demographics, cycles received prior to stem cell mobilization, CD34 blood counts prior to collection, total stem cell yield, mobilization failure rates, and subsequent attempts of mobilization

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

### 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 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, 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, tightness in the chest,

and low blood pressure , 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

### 11.4 Daratumumab

Among the 151 subjects treated with 16 mg/kg daratumumab as monotherapy in Studies GEN501 (NCT00574288) and MMY2002 (NCT01985126), the most frequently reported AEs (reported in >10% of subjects) were fatigue (29%); anemia (23%); nausea (19%); back pain (18%); cough (17%); thrombocytopenia (16%); decreased appetite (13%);

pyrexia, dyspnea, upper respiratory tract infection (12% each); nasal congestion and neutropenia (11% each). Grade 3 and higher AEs were reported in 48% of subjects treated with 16 mg/kg monotherapy daratumumab. The most frequently reported Grade 3 or higher AEs were anemia (13%) and thrombocytopenia (9%). All other Grade 3 and higher AEs were reported in <5% of subjects. No death has been reported in our ongoing daratumumab-KRd study using 36 mg/m$^2$ twice weekly dosing.

Among the 283 patients who received daratumumab in combination with lenalidomide and dexamethasone in the POLLUX trial[12], the most frequently reported AEs (reported in >10% of subjects) were neutropenia (59%), anemia (31%),thrombocytopenia(27%), febrile neutropenia (6%), lymphopenia (6%), diarrhea (43%), fatigue (35%), upper respiratory tract infection (32%), constipation (29%), cough (29%), muscle spasms (26%), nasopharyngitis (24%), nausea (24%), pyrexia (20%), insomnia (19%), dyspnea (18%), back pain (18%), vomiting (17%), asthenia (16%), peripheral edema (15%) and pneumonia (14%). The most frequently reported Grade 3 or higher AEs were neutropenia (52%), anemia (12%),thrombocytopenia(13%), febrile neutropenia (6%), lymphopenia (5%), diarrhea (5%), fatigue (6%) and pneumonia (8%). All other Grade 3 and higher AEs were reported in <5% of subjects.

Likely Side Effects: those occurring in more than 10% or more than 10 out of 100 persons who receive Daratumumab:

- Infusion related reaction (see separate section)
- Infection of the upper respiratory tract infection such as nose, sinuses throat or airway
- Infection of the lung
- Low neutrophils (a type of white blood cell)
- Low platelets
- Low red blood cells
- Low lymphocytes (a type of white blood cell)
- Numbness/tingling of the hands, feet or limbs
- Headache
- Cough
- Shortness of breath
- Diarrhea
- Nausea
- Vomiting
- Muscle spasms
- Fatigue
- Fever
- Swelling of hands, feet or limbs

Less Likely Side Effects: those occurring in 10% or 10 out of 100 persons who receive Daratumumab:

- The flu
- Sepsis (a life threatening condition that arises when the body's response to an infection injures its own tissues and organs)

- Irregular heartbeat

Rare and/or Potentially Serious Side Effects: these have occurred in less than 1% or in less than 10 out of 1,000 persons who receive Daratumumab:

- Shingles (Herpes zoster)
- High blood pressure
- Low oxygen
- Swelling of the throat
- Inflammation of lung tissue (pneumonitis)
- Difficulty with blood testing prior to blood transfusion (Indirect Antiglobulin Testing positive)

**Infusion Related Reactions**

Daratumumab is an antibody. An antibody is a large protein that is used by the immune system to identify and neutralize bacteria and viruses. A side effect to daratumumab that occurs during or shortly after an infusion is completed (when the medicine is given into a vein) is called an infusion-related reaction. Infusion–related reactions were reported in approximately half of all patients treated with daratumumab. It usually occurs with the first infusion and during or within the first few hours of the start of the infusion.

Signs and symptoms of infusion-related reactions may include respiratory symptoms, such as stuffy nose, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms are having trouble breathing (wheezing), runny nose, fever, chest discomfort, itching of the skin, and low blood pressure or high blood pressure. Most of the observed infusion-related reactions so far were mild or moderate, and ended by temporarily stopping the infusion and giving medicines to treat the side effect. Tell your doctor right away if you have above mentioned symptoms.

If you have a breathing problem now or had breathing problems in the past (like chronic obstructive pulmonary disease (COPD) or asthma), you should tell your study doctor. Also, if you start to have breathing problems while you are on the study you should tell your study doctor right away. You may be asked to see a doctor who takes care of patients with airway diseases, and additional medicines for airway problems may be given to you. Your doctor will explain how these additional medicines should be taken. Get emergency medical help if you have any of following: hives, wheezing, difficulty breathing, swelling of your face, lips, tongue, or throat or pain in chest.

Severe reactions have occurred, including narrowing and obstruction of the respiratory airway (bronchospasm), low oxygen, shortness of breath, high blood pressure, swelling in the throat and fluid accumulation in the lungs (pulmonary edema). Your study doctor and their staff will be ready to treat such a reaction in case it happens. In the future, you should tell any doctor you visit that you received daratumumab (an antibody) in this research study and if you had an allergic reaction including anaphylaxis, the worst case of allergic reaction.

The sponsor will continue to monitor infusion-related reactions and make changes to the way daratumumab is administered and/or recommend additional medications as necessary.

In this study, the following will be done to reduce the chance of a daratumumab infusion related reaction

- You will get medications, including steroids, acetaminophen and antihistamine, before the infusion.
- If you have a reaction, the infusion will be paused and the symptoms treated as needed. Dependent on the reaction, the infusion may continue at a slower rate. If you have a life-threatening reaction, you will need to stop further treatment with daratumumab and your doctor will discuss alternative treatments with you.
- If you are considered higher risk for breathing problems (for example COPD, asthma), you may also get medications, including inhaled steroids, after the infusion.
- You may stay overnight in hospital after the infusion so medical staff can check you.

**Blood Cell Effects**

Daratumumab may affect different types of blood cells.

- Low lymphocyte and neutrophil levels may be seen. Lymphocytes and neutrophils are types of white blood cells which are part of the body's immune response system which fights infections. This means that while you receive daratumumab, there may be a greater risk of getting an infection or getting a more severe infection. If you have an infection now, have a history of frequent infections, or if you feel sick, you should tell your study doctor right away. Signs of an infection may include fatigue, headache, fever, chills, aches and pains, coughing, congestion, chest tightness, or shortness of breath.
- Low platelet levels may be seen. Platelets help blood to clot. Low platelets may increase the risk of bleeding and bruising.

**Infection**

Different kinds of infection have been seen in patients receiving daratumumab. Most of them are upper respiratory tract infection. Majority of the observed infections so far were mild or moderate. Severe infection such as pneumonia and sepsis has also been reported. Herpes Zoster Virus infection (shingles) is an uncommon finding. Your doctor will tell you about how to prevent the Herpes Zoster Virus infection.

**Indirect Antiglobulin Testing**

If you need a blood transfusion, tests are performed on your blood so that suitable donor blood can be given for a transfusion. Daratumumab treatment will affect one of these tests known as an indirect antiglobulin test (IAT; also known as an indirect Coombs test). Therefore, an IAT will be done before you receive daratumumab and the result placed on the patient identification wallet card you will carry for this study. Before a blood transfusion, you should show the wallet card and tell all your health care

providers that you are taking daratumumab and that it interferes with pre-transfusion blood testing. You should do this during the entire period that are receiving daratumumab and for at least 6 months after your last daratumumab infusion or for as long as your study doctor recommends.

**What about birth control and pregnancy during the study?**

The effects of daratumumab on fertility, the human embryo, the fetus, or the breast-fed infant are unknown. If you are a woman, taking part in the study might harm your unborn child or breast-fed baby. Thus, you must agree not to become pregnant while you are in this study. Also, you cannot take part in this study if you are pregnant or breastfeeding a child. If you are a man, the effect of daratumumab on your sperm is unknown.

If you are a woman and becoming pregnant is a possibility, you will be required to undergo a pregnancy test prior to taking daratumumab. Both male and female patients must use effective methods of birth control during the course of the study and for 3 months after stopping daratumumab.

The type of birth control you use must be discussed with, and approved by, the study doctor before you begin the study. If you are female and become pregnant during the study, you must tell the study doctor immediately. You will have to stop taking part in the study. The study doctor will advise you about your medical care. We will ask you to allow us to collect information about your pregnancy and the health of your baby. If you are male, you should advise your study doctor if you father a child while participating in this study. The doctor will advise you on medical attention for your partner should this be necessary. We will ask for your partner's permission to collect information about the pregnancy and health of the baby.

If you are a woman:

- You must not donate eggs during the study and for 3 months after your last dose of study drug.

If you are a man:

- The effect of the study drug on your sperm is unknown.
- You must not donate sperm during the study and for 3 months after your last dose of study drug.

## 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 $\geq$10 mg/dL and abnormal kappa/lambda ratio (when primary determinant of response).

c) For patients with initial baseline 24-hr UPEP samples demonstrating ≥100 mg/24 hrs, patients will 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. This will be a centralized Next-Gen Sequencing (NGS) based MRD testing. Flow cytometry based assay to rule out MRD (defined as less than 20 abnormal plasma cells) in bone marrow aspirates of CR/sCR/VGPR patients. CR/VGPR and MRD $10^{-5}$ negative in the bone marrow is confirmed by using a validated method with a sensibility of at least 1 in $10^{-5}$ nucleated cells. Patients with <CR/sCR/VGPR are considered MRD positive. We will use the MSKCC flow cytometry MRD method which is based 10-colors in a single tube. This test has sensitivity to identify 1 myeloma cell in 100,000 bone marrow cells, or better. 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 8 cycles of DKRd. A patient with CR/sCR/VGPR who has undeterminable MRD status will be treated as MRD+ for the primary endpoint.

**Traditional Response Criteria from International Myeloma Working Group Criteria for Multiple Myeloma[65] (KUMAR ET AT, LANCET ONCOL 2016):**

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 <100 mg 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 >10 mg/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 clinician before being labeled as "relapse"[27,28].
     - Development of ≥ 5% light-chain restricted plasma cells in the bone marrow
     - Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, hypercalcemia

## MRD Response Criteria based on 2018 definition for Multiple Myeloma [22, 27, 28]

Evaluation of Response Criteria

a) VGPR/CR and MRD $10^{-5}$ negative in the bone marrow: absence of phenotypically aberrant clonal plasma cells by multicolor flow cytometry and/or next generation sequencing on bone marrow aspirates using a validated method with a sensitivity of at least 1 in $10^{-5}$ nucleated cells.

b) VGPR/CR but MRD positive in the bone marrow: VGPR/CR as defined above but with presence of phenotypically aberrant clonal plasma cells by multicolor flow cytometry and/or next generation sequencing on bone marrow aspirates using a validated method with a sensitivity of at least 1 in $10^{-5}$ nucleated cells.

c) Imaging plus MRD Negative: MRD negativity as defined by multicolor flow cytometry and/or next generation sequencing (as defined above) plus disappearance of areas of increased tracer uptake found at baseline or preceding PET/CT or decrease to less mediastinal blood pool SUV or decreased to less that that of surrounding normal tissue.

We note that while the IMWG includes both MFC and next generation sequencing in their response definition, only MFC will be used for our primary endpoint definition. Next generation sequencing will be investigated as a secondary endpoint.

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**

If a patient is removed off-study during cycles 1-4, the patient is considered not evaluable, which will allow another patient to replace this slot.

- 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.
- Patient has < PR after 4 cycles

**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

Primary Objective:

This is a phase II study to assess the efficacy of up to 8 cycles of combinational therapy with daratumumab, carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma (MM) patients. The primary objective of the study is to assess the rate of MRD negativity at the end of planned treatment up to 8 cycles for the combination therapy using multiparametric flow cytometry. Patients with < PR after completing 4 cycles will be included in the analysis of the primary objective and will be considered MRD positive. Patients who receive any study drug and have at least one post-baseline disease assessment will be considered evaluable for the primary endpoint. The rate of MRD negativity will be assessed for each cohort, separately.

This study is designed to distinguish between an unpromising MRD rate of 40% and a promising rate of 60% [1]. The unpromising rate of 40% is based on the 1st generation sequencing-based MRD rate in the referenced Korde et al study. The flow cytometry-based MRD assessment that will be used as part of this study has been shown to have similar performance as the sequencing-based MRD assessment used in that study.

The study includes two cohorts, which of each will receive up to 8 cycles of combination therapy. The two cohorts are defined based on the schedule and dosing of carfilzomib. These cohorts are described in Section 4.0. The following Simon two-stage design will be evaluated separately for the two cohorts.

Using a Simon's minimax two-stage design, the first stage of the study will enroll 28 patients. If at least 12 have a best response of MRD negativity within 8 cycles of therapy, the study will continue to enroll remaining patients up to a total of 41 patients. If, after 28 patients have accrued, it is uncertain whether the response threshold will be met, accrual will be held until the determination can be made. If 21 of the 41 patients have a best response of MRD negativity within 8 cycles of therapy the study will be considered to be successful. The study is designed to have a type I error and a type II error of 0.10. The maximum sample size is 41 patients.

The study includes safety suspension rules; throughout the study we will monitor for grade 3 or higher heart failure. These safety suspension rules will be applied separately in the two cohorts. In the event that the rule is crossed (see Table below), the study will be suspended for that cohort and all safety data will be reviewed by the PI. We will report all SAEs per standard guidelines (Section 17.2). In addition, throughout the study we will monitor for grade 4 or higher adverse events related to study drugs; if the PI notices there is a safety signal, the study will be suspended and all safety data will be reviewed by the PI.

| **Failure Type** | **# of failures needed to suspend the study** | **Failure rate in the population** | **Probability boundary is crossed** |
|---|---|---|---|
| Heart failure/Ischemic heart disease (grade 3 or higher) Or grade 4 or higher adverse events due to study drug. | 3 in the first 17 patients<br>4 in the first 29 patients | 0.05 | 0.1 |
| | 5 patients at any point | 0.2 | 0.95 |

The above numbers apply for each of the cohorts. Each cohort will be assessed independently.

Secondary Objective. Objectives 1, 2, and 3 below will be evaluated separately for the two cohorts.

1. To evaluate the safety and tolerability of the combination therapy. Toxicities will be summarized by grade and cycle of therapy. Patients who receive any study drug will be included in this assessment.
2. To evaluate the rates of best overall response (partial response (PR) or better), very good partial response (VGPR) or better, and complete response (CR) or stringent CR (sCR) for the evaluable patients. See section 12.0 for response definitions. Response proportions along with exact 95% confidence intervals will be reported.
3. Kaplan-Meier methods will be used to estimate overall and progression-free survival. . Patients who receive any study drug will be included in this assessment.
4. To compare MRD techniques of multi-parametric flow cytometry with 1) next-generation sequencing and 2) mass spectrometry using summary statistics. Rates of concordance for the measures will be estimated. This will be evaluated among all MRD assessments.
5. To create a bone marrow, urine, stool, and peripheral blood sample bank. These samples may be used to later evaluate biological activity of daratumumab, 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, stool, bone marrow aspirates) associated with clinical outcomes.

Exploratory Studies:

1. The gene panel myTYPE (or alternative equivalent platform) will explore whether any mutations appear to be associated with response to therapy or toxicity associated with therapy. 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. myTYPE (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.

3. To evaluate the effects on stem cell mobilization quality in patients receiving daratumamab, carfilzomib, lenalidomide, and dexamethasone. Examples of data being collected but not limited to will include the following: number of patients undergoing stem cell mobilization, demographics, cycles received prior to stem cell mobilization, CD34 blood

counts prior to collection, total stem cell yield, mobilization failure rates, and subsequent attempts of mobilization.

The proposed study will enroll 41 newly diagnosed multiple myeloma patients seen at MSKCC into each of the two cohorts. Currently, we see over 250 new patients per year and we anticipate enrolling 2-4 patients per month on this study. Thus, we expect to have the study fully enrolled 12-24 months after opening of the study.

## 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

The research nurse (Clinical Research Nurse, CRN) will be responsible for confirming eligibility and assisting the MD with the registration process. All study data will be collected by an assigned data manager (Clinical Research Coordinator, 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.

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

Regular 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: https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

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 indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

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 performed, 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 consultation. 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.

**Use of research 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

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to appropriate authorities, such as the FDA by the SAE staff through the IND Office

**17.2.1**

**AE/SAE Reporting by Investigator-sponsor to Janssen**

As the sponsor of the Study, PRINCIPAL INVESTIGATOR shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this section, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The PRINCIPAL INVESTIGATOR will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as defined within this section.

This Study has been designated as an interventional study. As such, all adverse events for daratumumab regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

**Reporting to Amgen**

Serious Unexpected Suspected Adverse Reactions (SUSARs) will be reported to Amgen.

Pregnancy/Lactation exposures should be reported to Amgen within **10 calendar days** of Sponsor awareness.

Amgen Global Safety reporting information for SUSARs and Pregnancy/Lactation exposures:
- Electronically via Amgen SECURE Email service (preferred) : svc-ags-in-us@amgen.com
- Facsimile (fax) to: 1-866-451-0371

**Adverse Event (AE) Definition:**

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can

therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

**Adverse Event of Special Interest Definition:**

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Infusion reactions ≥ Grade 3
- Infections ≥ Grade 4
- Cytopenias ≥ Grade 4
- Tumor lysis syndrome
- Other malignancies
- Intrvascular hemolysis – all grades

Any Adverse Event of Special Interest that is to be reported to the COMPANY should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of knowledge of the event.**

**Individual Case Safety Report (ICSR) Definition:**

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

**Product Quality Complaint (PQC)**

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

**Serious Adverse Event (SAE)**

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

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

**NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.**

**Hospitalization**

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be

considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

- [For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.]

**Life-Threatening Conditions**
Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

**Unlisted (Unexpected) Adverse Event/Reference Safety Information**

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether it is listed in the applicable product information.

http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf

For DARZALEX™ (daratumumab),the expectedness of an adverse event will be determined by whether it is listed in the Investigator's Brochure

**Special Reporting Situations**

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

**Pregnancy**

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR **within 24 hours of becoming aware of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

**Maintenance of Safety Information**

All safety data should be maintained in a clinical database in a retrievable format. The PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

**Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen Scientific Affairs, LLC**

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed up in accordance with clinical practice.

**SAEs, Adverse Events of Special Interest (AESI), and Special Reporting Situations**

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

- The event resolves

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

The PRINCIPAL INVESTIGATOR will transmit all SAEs, AESIs, and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 10,Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs, LLC.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, **within 24 hours becoming aware**, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, AESI, serious ADR or special situation is required.

- The PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in Section 10 from this Exhibit within **24 hours of such report or correspondence being sent to applicable health authorities.**

**Non-Serious AEs**
All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

**PQC Reporting**

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

**Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products**

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the PRINCIPAL INVESTIGATOR should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

**Transmission Methods**

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred) : IIS-BIO-VIRO-GCO@its.jnj.com
- For business continuity purposes, if SECURE Email is non-functional:
    - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report: to 1-866-451-0371

Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

## 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 and 90 days after the last dose of carfilzomib, even if he has undergone a successful vasectomy. Male patients must refrain from donating sperm for at least 90 days after the last dose of carfilzomib. 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; 4) for at least 28 days after lenalidomide discontinuation; and 5) for at least 30 days after the last dose of carfilzomib. 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 methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

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

## Pregnancy testing

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

## Before starting lenalidomide

*Female Patients:*

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

*Male Patients*:

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

## During study participation and for 28 days following lenalidomide discontinuation

*Female Patients:*

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

*Male Patients:*

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

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

## APPENDIX 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 *myTYPE* involves massively parallel sequencing, coupled with solution-phase exon capture. The assay will generate high-depth (~1500x) sequencing data for genes causally implicated in myeloma pathogenesis by comprehensive whole exome and whole genome studies. Genes have been selected on the basis of known mutation frequencies in myeloma neoplasms and prior evidence from genomic profiling studies including copy number analysis. *myTYPE* contains genome wide copy number probes, which supports detection of arm level copy number alterations as well as hyperdiploid genomes and the detection of IGH rearrangements. Thus, using *myTYPE* we will establish in-house algorithms to deliver full genome annotation and definition of clonal and subclonal mutation clusters. For studies focusing on characterization of MRD+ cells, samples will be sorted of FACS-Aria Fusion and RNA and DNA will be extracted for bulk sequencing. Clonal architecture of residual disease will be evaluated by single cell transcriptome analysis. The targeted DNA sequencing panel *myTYPE* covers the following:

- Copy number analysis: by including genome wide SNPs at least every 3Mbs
- IgH translocations: by including the hotspot intron In IgH where the vast majority of breakpoints occur
- Amplifications and deletions: we are adding additional SNPs for common amplification and deletions in myeloma, both for chromosomal regions and specific genes i.e. 1q gain and 17p deletion, *MYC* amplification, *CKS1B* amplification, *TP53* deletion, and more.
- Genes (exons) with previously reported recurrent mutations, i.e. *KRAS, NRAS, BRAF, FAM46C, IRF4, TRAF3, TP53, CYLD, DIS3,* and many more (in total ~110 genes). In addition, we are adding previously mutated and candidate genes in treatment target pathways, i.e. the cereblon pathway, NFKB and BCR pathways, genes within proteasome subunits, as well as targets for novel immunotherapy.

## APPENDIX C

### Contraception/Female

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

### Contraception/Male

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