Bristol Myers Squibb™

Dr. Manisha Bhutani
LEVINE CANCER INSTITUTE C,
1021 MOREHEAD MEDICAL DR

November 30, 2023

Dear Dr. Manisha Bhutani,

Direct to Patient (DtP) shipments
Protocol Number: RV-CL-MM-PI-12836

This is an update to the letter that was dated Nov 6th regarding Direct to Patient (DtP) shipments. BMS has decided to discontinue the "Direct to Patient" (DtP) service provided by McKesson, which was implemented in response to COVID-19. This service allowed Sponsor ISR sites to request McKesson to ship Clinical supplies directly to patients. McKesson will resume shipping Clinical supplies to sites only, for applicable hCelgene ISRs that include any of the following IMiDs: Lenalidomide, Revlimid, Pomalidomide.

All services provided by McKesson before the pandemic will remain unchanged.

Additionally, please disregard the statement in the previous letter that investigational sites will no longer be able to use their own courier to transfer IMP from site to the patient's home. This statement should not have been included as the letter was intended to only address BMS/McKesson closing the COVID emergency response Direct to Patient (DtP) shipment arrangement for clinical supply of IMiDs only.

Please be reminded that as the Sponsor of the study, you hold responsibility to follow applicable guidance, the protocol and be in alignment with its defined evaluations for safety, pregnancy, and overall patient assessments for any patient requested shipments. This change should be implemented as soon as possible, as no further McKesson direct to patient shipments of Clinical supplies will be authorized as of January 1, 2024. If you have any questions/concerns, please feel free to reach out to me.

Sincerely,
Divya Upadhyay
Study Manager

Divya Upadhyay,
Study Manager |
BMS Investigator Sponsored Research Program

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Bristol Myers Squibb™

Dr. Manisha Bhutani
LEVINE CANCER INSTITUTE C,
1021 MOREHEAD MEDICAL DR

November 6, 2023

Dear Dr. Manisha Bhutani

Direct to Patient (DtP) shipments

BMS has taken the decision to close the "Direct to Patient" (DtP) service provided by McKesson. This service allowed the transfer of Investigational Medicinal Product (IMP) to the patient's home as part of the BMS emergency response to the global COVID-19 pandemic.

Due to the end of the COVID-19 emergency response, this service will no longer be an option.

Additionally, investigational sites will no longer be able to use their own courier to transfer IMP from site to the patient's home. These changes will take effect immediately.

If you have any questions/concerns, please reach out to your BMS Global Trial Manager/Trial Manager contact, contact information below in footer.

Sincerely,
Divya Upadhyay
Study Manager

Divya Upadhyay,
Study Manager |
BMS Investigator Sponsored Research Program

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Protocol #: LCI-HEM-MYE-KRdD-001
TITLE: Phase II Study of Daratumumab Combined with Carfilzomib, Lenalidomide and Dexamethasone in Newly Diagnosed Multiple Myeloma

Coordinating Center:
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Trial Supported by:
Janssen Scientific Affairs, Inc., Amgen Inc. and Celgene Corporation

Investigational New Drug (IND) # 144160

The study will be conducted in compliance with the protocol, ICH/GCP and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) are not displayed. Hence, the appearance of product names without these symbols does not imply that these names are not proprietary.

PROTOCOL SIGNATURE PAGE
Phase II Study of Daratumumab Combined with Carfilzomib, Lenalidomide and Dexamethasone in Newly Diagnosed Multiple Myeloma

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

_____ _____
Signature of Sponsor-Investigator Date

Manisha Bhutani, M.D

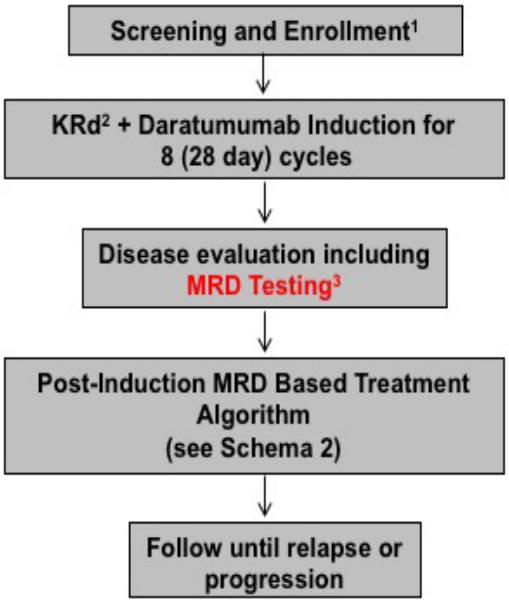
SYNOPSIS

TITLE	**Phase II Study of Daratumumab Combined with Carfilzomib, Lenalidomide and Dexamethasone in Newly Diagnosed Multiple Myeloma**
STUDY POPULATION	Newly Diagnosed Multiple Myeloma (NDMM)
PHASE	II
SUMMARY OF STUDY RATIONALE	Daratumumab is a first-in-class, human IgG1 monoclonal antibody that binds CD38-expressing malignant plasma cells with high affinity and induces tumor cell death through diverse mechanisms and is approved for the treatment of relapsed/refractory MM. The regimen of carfilzomib, lenalidomide and dexamethasone (KRd) is a highly active regimen used in the treatment of NDMM. The immunomodulatory effects of KRd have a strong potential for synergy with those of daratumumab, and preliminary data from a Phase I trial of KRd+daratumumab support the safety of this combination. Post induction, the treatment course for NDMM varies. While assessment of minimal residual disease (MRD) status post treatment is increasingly common, data on its utility as a tool to select the optimal post-induction therapy are not yet available.
STUDY DESIGN	This single arm, two-stage, open-label Phase II study is designed with the primary objective of evaluating the efficacy of induction therapy comprised of 8 cycles of carfilzomib, lenalidomide, dexamethasone and daratumumab (KRd+daratumumab) in terms of complete response or better (≥ CR) in subjects with NDMM and comparing to relevant historical controls (see Schema 1). Post induction, all subjects will undergo disease evaluation, including assessment of minimal residual disease (MRD). Post-induction disease evaluation will be followed by an MRD-based treatment algorithm (see Schema 2). This trial will allow us to gather preliminary data on use of MRD status to direct post-induction therapy.
OBJECTIVES	<u>Primary Objective:</u> • The primary objective is to evaluate the efficacy of daratumumab when combined with KRd as induction chemotherapy, in terms of complete response or better, in subjects with newly diagnosed multiple myeloma. <u>Secondary Objectives:</u> • Evaluation of daratumumab when combined with KRd by estimating Progression-free survival (PFS), Overall survival (OS), Time to disease progression (TTP), Overall response rate (ORR), Duration of response (DoR), Time to next treatment (TTNT).

KEY INCLUSION CRITERIA	• Newly diagnosed multiple myeloma (NDMM) as per the IMWG 2014 criteria
	• No more than 1 prior cycle of systemic therapy (to accommodate subjects who needed emergent treatment at diagnosis)
	• Age ≥ 18 years
	• ECOG ≤ 2
	• Measurable disease:
	  o Serum M-protein ≥1 g/dL (≥ 0.5 g/dL for IgA or IgM) **OR**
	  o Urine M-protein ≥200 mg/24 h **OR**
	  o Involved free light chain (FLC) level ≥10 mg/dL provided serum FLC ratio is abnormal
	• Adequate organ and bone marrow function
	• Negative serum pregnancy test in females of childbearing potential (FCBP)
	• Willingness to use required birth control as applicable

STATISTICAL CONSIDERATIONS	The primary objective is to evaluate the efficacy of daratumumab when combined with KRd, in terms of complete response or better, in subjects with newly diagnosed multiple myeloma, and compare to relevant historical controls. For the NDMM patient population, 8 cycles of KRd induction provides a complete response or better rate of approximately 50%. For this population of patients treated with KRd+daratumumab, the aim is to achieve a rate of CR or better of 70%. A minimax 2-stage design will be used to test the hypothesis that the CR or better rate is less than or equal to 50%. Twenty-three (23) subjects will be enrolled in the first stage, and if at least 12 of the 23 subjects have a complete response or better after induction therapy, an additional 16 subjects will be enrolled (a total of 39 patients). If at least 24 of 39 subjects have a complete response or better, the null hypothesis will be rejected. Based on a one-sided alpha = 0.10 significance level, this sample size will provide 90% power to reject the null hypothesis, assuming the true complete response or better rate is 70%.
TOTAL NUMBER OF SUBJECTS	Up to 39

SCHEMA 1: STUDY OVERVIEW



[1]Two-stage design: enroll 23 in Stage 1: If at least 12 experience a complete response or better at post-induction disease evaluation, enroll 16 in Stage 2 (**NOTE**: Stage 1 subjects will continue to be followed through post-induction treatment regardless of whether Stage 2 opens)

[2]KRd=carfilzomib, lenalidomide, dexamethasone

[3]MRD=minimal residual disease

Note: MRD testing will only be performed in subjects with VGPR or better; subjects with less than VGPR will be considered MRD+ without performing the test

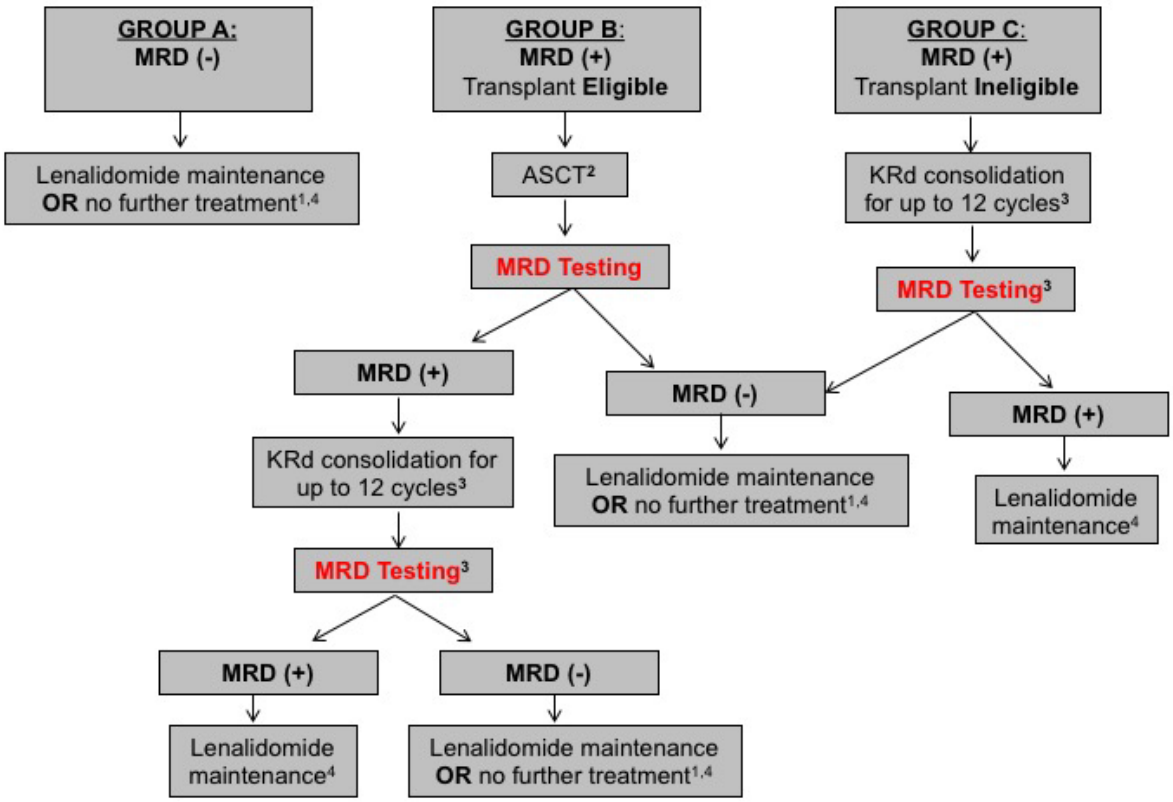
Note: For subjects who completed a pre-study cycle of induction chemotherapy, only 7 cycles of KRdD Induction should be given.

SCHEMA 2: POST-INDUCTION MRD BASED TREATMENT ALGORITHM

After induction, all subjects will undergo disease evaluation. Those who experience ≥VGPR will undergo an assessment of minimal residual disease (MRD) and will be classified as MRD (+) or MRD (-). Those with <VGPR will be considered to have MRD (+) disease and will follow MRD (+) algorithm.

Subjects who do not have an adequate baseline NGS MRD sample (for whatever reason) will be considered MRD unevaluable and will receive treatment as though MRD + for all subsequent MRD time-points and will not have subsequent protocol directed NGS MRD samples collected.

NOTE: MRD will be evaluated via flow cytometry and DNA sequencing. Based on MRD results evaluated via DNA sequencing, subjects will be divided into 3 separate treatment groups. All subjects in each group will be followed until relapse or progression.



[1]At discretion of investigator; maintenance therapy continued until relapse, progression or intolerance
[2]ASCT = autologous stem cell transplant
[3]KRd=carfilzomib, lenalidomide, dexamethasone; The # of cycles will be dependent on MRD status which will be tested after cycle 4, 8 and 12; those who convert to MRD (-) will discontinue KRd and receive lenalidomide maintenance or no further treatment at discretion of investigator
[4]All subjects will be followed until relapse or progression

Note: The 10^{-5} MRD result from the NGS MRD test will be used for treatment decisions

If a subject does not have an NGS test report available (for whatever reason), the subject will be assumed to be MRD + and will receive treatment as though MRD+ per the algorithm.

LIST OF ABBREVIATIONS

Abbreviation	*Spelled out abbreviation*
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
AML	Acute myeloid leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARDS	Acute respiratory distress syndrome
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BCR	B cell receptor
BM	Bone marrow
BSA	Body surface area
BUN	Blood urea nitrogen
CBCD	Complete blood count with differential and platelets
CDC	Compliment-dependent cytotoxicity
CFR	Code of Federal Regulations
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CRAB features	Calcium elevation, renal failure, anemia, lytic bone lesions
CrCl	Creatinine clearance
CTCAE	Common terminology criteria for adverse events
CTMS	Clinical Trial Management System

Dara-SC	Daratumumab Subcutaneous
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ESA	Erythropoietic stimulation agents
ESI	Event of special interest
F-FDG PET	F-fluorodeoxyglucose PET
FCM	Flow cytometry
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FLC	Free light chain
FCBP	Females of child bearing potential
GCP	Good clinical practice
GMP	Good manufacturing practice
HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface antigen
HSCT	Haploidentical stem cell transplant
HDC	High dose chemotherapy
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICSR	Individual case safety report
ICH	International Council on Harmonisation

IFE	Immunofixation
IMiD	Immunomodulatory agent
IMP	Investigational Medicinal Product
IMWG	International Myeloma Working Group
IPM	Initial primary malignancy
IRB	Institutional Review Board
IRR	Infusion related reactions
IV	Intravenously
Kd	Carfilzomib plus dexamethasone
KRd	Carfilzomib, lenalidomide and dexamethasone
LCI	Levine Cancer Institute
LDH	Lactate dehydrogenase
LTD	Last tolerated dose
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic syndrome
MFS	Multiparameter flow cytometry
MM	Multiple myeloma
MPD	Maximum planned dose
MRD	Minimal residual disease
MTD	Maximum tolerated dose
MUGA	Multi gated acquisition scan
NCI	National Cancer Institute
NDMM	Newly Diagnosed Multiple Myeloma
NGF	Next generation flow
NGS	Next generation sequencing
NIH	National Institutes of Health
NK	Natural killer

NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PET/CT	Positron emission tomography/computed tomography
PFS	Progression free survival
PML	Progressive multifocal leukoencephalopathy
PO	By mouth
POEMS	Polyneuropathy organomegaly endocrinopathy monoclonal gammopathy and skin changes
PQC	Product quality complaints
PRES	Posterior reversible encephalopathy syndrome
QIg	Quantitative immunoglobulins
RBC	Red blood cells
Rd	Lenalidomide/dexamethasone
REMS	Risk evaluation and mitigation strategy
SADR	Serious adverse drug reaction
SAR	Suspected adverse reaction
SC	Subcutaneous
sCR	Stringent complete response
SAE	Serious adverse event
SJS	Stevens-Johnson Syndrome
SPD	Sum of the products of the maximal perpendicular diameters of measured lesions
SPM	Secondary primary malignancy
SOP	Standard operating procedures

SPEP	Serum protein electrophoresis
SUSAR	Suspected unexpected serious adverse reaction
SUV_{max}	Maximum standardized uptake value
SVR	Sustained virologic response
TCR	T cell receptor
TEAEs	Treatment emergent adverse events
TEN	Toxic epidermal necrolysis
TH1	Type 1 T helper
TLS	Tumor lysis syndrome
TMA	Thrombotic microangiopathy
TTNT	Time to next treatment
TTP	Time to progression
TTP/HUS	Thrombotic thrombocytopenic purpura/Hemolytic uremic syndrome
UAP	Unanticipated problem
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
Vd	Bortezomib plus dexamethasone
VGPR	Very good partial response
WB-MRI	Whole body magnetic resonance imaging
WBC	White blood cell

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1 Multiple Myeloma (MM)

Multiple myeloma (MM) is a neoplasm of plasma cells that is characterized by osteolytic bone lesions and organ damage, such as hypercalcemia, anemia, and renal insufficiency. Despite major advances in therapy, MM is still considered an incurable malignancy. The introduction of immunomodulatory agents (IMiDs; e.g., lenalidomide) and proteasome inhibitors (e.g., bortezomib, carfilzomib), coupled with advances in autologous stem cell transplant (ASCT) have improved progression free survival (PFS) and overall survival (OS) for MM patients. Unfortunately, the majority of patients still suffer relapses with progressively shorter disease-free intervals with each relapse.

Relapse in MM, including in those who achieve a complete response (CR) post treatment, is likely due to the presence of minimal residual disease (MRD) undetectable by standard disease evaluation methods (i.e., assessment of monoclonal proteins in serum and urine and evaluation of bone marrow). Regardless of how MRD is measured, studies have consistently shown that MRD negative (-) disease is associated with better long-term outcomes in patients who achieve a complete response [1]. The International Myeloma Working Group (IMWG) defines MRD (-) as absence of clonal plasma cells either by flow cytometry (flow) or next-generation sequencing (NGS) provided the validated assay used has a minimum sensitivity of 1 per 10^5 nucleated cells [1]. This assay was recently approved by the FDA, on September 28th, 2018. The results are indicated to be interpreted by qualified healthcare professionals in accordance with professional guidelines for clinical decision-making in conjunction with other clinicopathological features. Increasingly, MRD is being assessed at the time of response evaluation (within and outside of clinical trials) to help further refine the depth of response achieved, and to potentially identify those patients who may (or may not) need additional therapy.

Currently, the typical treatment algorithm for good performance status patients with active MM includes induction chemotherapy typically comprised of 3 drugs. Post induction newly diagnosed (ND) MM patients may proceed to observation, maintenance therapy with single agent lenalidomide, or consolidation. Consolidation includes either high dose chemotherapy and ASCT in transplant eligible patients, or continuation of the same regimen used for induction. Consolidation may be followed by maintenance therapy, usually lenalidomide as a single agent continued until relapse or progression [31].

Common triplet induction regimens that can be used in transplant and non-transplant candidates include bortezomib/lenalidomide/dexamethasone, and carfilzomib/lenalidomide/dexamethasone [31].

1.2 Carfilzomib (Kyprolis®), Lenalidomide (Revlimid®), Dexamethasone (KRd) in MM

Carfilzomib is an epoxomicin derivative with the ability to irreversibly inhibit proteosomes. It has been shown in preclinical and early clinical studies to have activity in MM [2]. In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib [3]. Pre/post carfilzomib in vivo pharmacogenomics gene expression

profiling data from the University of Arkansas Car-505 protocol (unpublished data) suggests that the use of carfilzomib may impact the more proliferative and high risk MM sub-clone in a given patient, whereas this effect was not seen with the proteasome inhibitor bortezomib [4].

1.2.1 Relapsed/Refractory

The combination of carfilzomib (**K**yprolis®) with lenalidomide (**R**evlimid®) and **d**examethasone (a regimen termed "KRd") initially exhibited excellent clinical activity in a phase Ib/II clinical trial in relapsed/refractory MM patients. In the dose escalation portion of the study (n=40), no maximally tolerated dose (MTD) was identified, and the maximum planned dose (MPD; 27mg/m^2 of carfilzomib) was recommended for the phase II portion (with an initial dose of 20mg/m^2 on days 1 and 2 of cycle 1, with the overall dosing regimen defined as 20/27 mg/m^2). The overall response rate (ORR) across the dose escalating cohorts was 62.5% [5]. In the phase II portion, 52 patients were enrolled and treated with the combination at the MPD for carfilzomib. The ORR in this cohort was 76.9%, and the median PFS was 15.4 months [6]. This trial was followed by the open-label phase 3 trial (ASPIRE) trial, wherein KRd was compared to Rd in patients with relapsed MM. Median PFS was significantly improved with the triplet (26.3 months compared to 17.6 months, p=0.0001). Median OS was not yet reached at the time of the analysis, but the OS rate at 24 months favored the triplet (73.3% versus 65%, p=0.04). Notably, patients in the KRd arm reported better quality of life as compared to the Rd arm [7].

1.2.2 KRd in NDMM Without ASCT

KRd has also demonstrated unprecedented depth of response in NDMM in several clinical trials. In a phase I/II study of KRd in NDMM patients, 53 subjects received up to 24 monthly cycles of KRd, with lenalidomide recommended as maintenance therapy off protocol. Grade ≥ 3 AEs included hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%) and neutropenia (17%).

Across all dose cohorts and after 8 cycles of KRd (n=44), the percent who achieved a complete response (CR) and stringent CR (sCR) was 34% and 30% respectively. The corresponding numbers after 18 cycles were 59% and 51%, respectively. The 2-year PFS was 92% [8,9]. The MPD of carfilzomib (20/36mg/m^2) was achieved and administered to 36 of the 53 subjects. Of the 36 who received this dose of carfilzomib, the rate of sCR after 8 cycles was 43% (reported in supplemental Table 1 from reference 8).

Korde and colleagues evaluated 8 cycles of KRd as induction (at a carfilzomib dose of 20/36 mg/m^2) in 45 patients with NDMM, followed by 24 cycles of lenalidomide in subjects who achieved at least stable disease post induction. The most common ≥ Grade 3 adverse events (AEs) reported in the NDMM group included hematologic toxicities: lymphopenia (76%), thrombocytopenia (24%), leukopenia (20%), anemia (27%), neutropenia (33%), and non-hematologic toxicities: electrolyte or metabolism disorders (36%).

After 8 cycles of KRd, 90% (38 of 42 evaluable patients) had at least a very good partial response (VGPR), with 28 (43%) achieving ≥ CR. The rate of MRD (-) was 100% among the 28 patients who achieved at least a CR, and as measured via flow; of the 21 who had MRD evaluated via NGS, 67% were MRD (-) [10]. MRD status was significantly associated with outcome; 12-month PFS for MRD (-) by NGS was 100% versus 95%, p=0.02.

1.2.3 KRd in NDMM with ASCT

To evaluate the effect of incorporating ASCT into the KRd regimen, 72 NDMM patients eligible for transplant received 4 monthly cycles of KRd at a dose of 20/36mg/m^2 followed by high dose chemotherapy and ASCT, 4 cycles of KRd as consolidation, and up to 10 additional cycles of KRd as maintenance. Lenalidomide monotherapy was recommended for maintenance therapy off protocol after the last cycle of KRd. As of January 2016, and at the end of KRd consolidation (i.e., after 8 cycles), CR was achieved in 73% and sCR was achieved in 69% (n=66) which increased to 82% at the end of KRd maintenance (n=44). At the end of KRd consolidation, 82% (of 33 patients evaluated) and 66% (of 29 evaluated) were MRD (-) after flow and NGS, respectively. After a median follow-up of 17.5 months, the 2-year PFS was 97% for all 76 patients [11]. Of the MRD (-) group (by NGS and/or flow) at the end of KRd consolidation, the 2-year PFS was 100%.

In a similar trial conducted in France, 46 patients were enrolled in a phase II study that included 4 cycles of KRd induction followed by high dose chemotherapy and ASCT. After hematologic recovery, 4 additional cycles of KRd were administered as consolidation followed by 1 year of lenalidomide maintenance. Post consolidation, 27 of 42 evaluable patients were in sCR (~64%) [12].

The data on KRd in NDMM while preliminary, are promising, particularly when combined with an ASCT as part of induction therapy. Despite the promising rates of sCR, however, there is still significant room for improvement in the treatment of NDMM.

1.3 Daratumumab and Daratumumab+ Hyaluronidase-fihj

Daratumumab is a first-in-class, human IgG1 monoclonal antibody that binds CD38-expressing malignant plasma cells with high affinity and induces tumor cell death through diverse mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, and induction of apoptosis.

Daratumumab IV is currently approved by the Food and Drug Administration (FDA) as monotherapy in patients with MM who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an IMiD, or who are double refractory to both these classes of drugs, and in combination with lenalidomide and dexamethasone (D-Rd), or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy[41]. Daratumumab is approved with the combination of carfilzomib and dexamethasone (D-Kd) in patients who have received one to three prior lines of therapy, and in combination with pomalidomide and dexamethasone (D-Pd) in patients who have received at least two prior lines of therapy including lenalidomide and a proteasome inhibitor [42]. Daratumumab is also approved for use in combination with bortezomib, melphalan and prednisone (D-VMP), for patients who are newly diagnosed but cannot receive an autologous stem cell transplant, as well as the combination of bortezomib, thalidomide, and dexamethasone (D-VTd) for patients who are newly diagnosed and eligible to receive an autologous stem cell transplant [42].

Daratumumab +hyaluronidase-fihj injection (DARZALEX FASPRO™) is given subcutaneously into the abdomen, and was recently approved by the Food and Drug Administration (FDA) in 2020 [41]. It was developed with the goal of decreasing administration times and rates of IRRs in MM patients [40]. Daratumumab SC is currently approved as monotherapy in patients with MM who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an IMiD, or who are double refractory to both these classes of drugs. Daratumumab +hyaluronidase-fihj is also indicated for newly diagnosed MM in combination with lenalidomide and dexamethasone (D-Rd), or bortezomib and dexamethasone (D-Vd), for the treatment of patients with MM who have received at least one prior therapy. It is also approved in combination with bortezomib, melphalan and prednisone (D-VMP) in newly diagnosed patients who are ineligible for an autologous stem cell transplant [41].

For the most comprehensive nonclinical and clinical information regarding daratumumab or daratumumab+ hyaluronidase, refer to the latest versions of the Investigator's Brochures. Also refer to the latest version of the prescribing information for daratumumab and daratumumab+hyaluronidase, and to Section 10.1.

1.3.1 Daratumumab Pharmacokinetics

The clinical pharmacology assessment of daratumumab SC monotherapy data are available from daratumumab SC-dosed subjects in a Phase 1/1b study MMY1004 [Part 2]) and Phase 3 study (MMY3012), Phase 2 combination therapy study MMY2040 and population pharmacokinetics and exposure-response analyses. In MMY1004, the 1800 mg dose achieved maximum Ctrough (Cycle 3 Day 1 predose) values that were similar or greater than the maximum Ctrough observed for the approved 16 mg/kg IV dose following the same dose schedule. The PK data from Part 2 supported the daratumumab SC 1800 mg dose selection for the Phase 3 study. The PK data from MMY3012 study demonstrated that daratumumab SC 1800 mg is non-inferior to daratumumab IV 16 mg/kg in terms of maximum Ctrough (Cycle 3 Day 1 predose), with the lower bound of the 90% CI for the geometric means ratio for daratumumab SC versus daratumumab IV for maximum Ctrough (Cycle 3 Day 1 predose) exceeding 80%, thereby meeting the predefined non-inferiority criterion.

Additionally, daratumumab SC 1800 mg monotherapy consistently produced lower peak-to-trough fluctuations, similar or slightly higher trough levels over time, and lower peak concentrations compared with daratumumab IV 16 mg/kg monotherapy. Overall, consistent daratumumab concentrations were observed across the body weight ranges. As expected, slightly higher concentrations were observed for subjects with lower body weights. There was no apparent relationship between exposure and safety endpoints (SAEs, Grade 3 or higher TEAEs and neutropenia).

The simulated trough concentrations following 6 weekly doses of daratumumab SC 1800 mg for combination therapy (daratumumab SC, bortezomib, melphalan, and prednisone [D-VMP], daratumumab SC, lenalidomide, and dexamethasone [D-Rd], daratumumab SC, bortezomib, lenalidomide, and dexamethasone [D-VRd]) were similar to monotherapy.

Overall, daratumumab SC was well-tolerated with manageable side effects and a significantly reduced incidence of IRRs relative to daratumumab IV. The safety profile of daratumumab

administered subcutaneously at a flat dose of 1800 mg continued to be generally comparable to that of the 16 mg/kg IV formulation [43].

1.3.2 Daratumumab Nonclinical Studies

DARZALEX FASPRO™ for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs). No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose. There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses [41].

1.3.3 Daratumumab Clinical Studies

The approval of daratumumab-SC was based on findings from the COLUMBA (MMY3012) study, a phase 3, non-inferiority, randomized, multicenter, open-label clinical trial which showed that the maximum Ctrough (Cycle 3 Day 1 predose) and overall response rate to SC daratumumab were non-inferior to IV daratumumab in subjects with relapsed or refractory multiple myeloma with considerably lower IRRs and reduced administration [40].

1.3.3.1 Daratumumab Monotherapy

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA *[see Clinical Trials (14.2)].* Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 26% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than 1 patient were general physical health deterioration, septic shock, and respiratory failure. Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia. Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia.

The most common adverse reaction (≥20%) was upper respiratory tract infection [41].

1.3.3.2 FDA Approved Daratumumab Combinations

The FDA approval of daratumumab in combination regimens for the treatment of MM was based on safety and efficacy data from two randomized phase 3 trials. The primary endpoint in both trials was PFS.

Daratumumab + Lenalidomide and Dexamethasone

The POLLUX trial (also known as MMY3003), randomized 569 patients who had received ≥ 1 prior line of therapy to lenalidomide and dexamethasone alone or in combination with daratumumab [16]. Based on a protocol-specified interim analysis, PFS at 12 months was significantly improved in the daratumumab group (83.2%) compared to the control group (60.1%) after >7 cycles of therapy. Both the ORR and the rate of ≥CR were also significantly higher in the daratumumab group (92.9% versus 76.4%, $p<0.001$ and 43.1% versus 19.2%, $p<0.001$). In the daratumumab group, 22.4% of patients were MRD (-) as compared with 4.6% in the control group ($p<0.001$); MRD (-) disease was also associated with longer PFS.

The most frequently reported TEAEs (≥20%) in the daratumumab group were neutropenia (59.4%), infusion reactions (47.7%), diarrhea (42.8%), fatigue (35.3%), upper respiratory tract infection (31.8%), anemia (31.1%), constipation (29.3%), cough (29%), thrombocytopenia (26.9%), muscle spasms (25.8%), nasopharyngitis (24%), nausea (24%) and pyrexia (20.1%). The most common (≥10%) ≥ Grade 3 TEAEs in the daratumumab arm were neutropenia (51.9%), thrombocytopenia (12.7%) and anemia (12.4%). The rates of AEs that led to treatment discontinuation were similar between the two arms of this trial.

Daratumumab + Bortezomib and Dexamethasone

Similar results were observed in the CASTOR trial (also known as MMY3004), which compared the combination of daratumumab, bortezomib, and dexamethasone with bortezomib and dexamethasone in 498 patients who had received ≥ 1 prior line of therapy [17]. Based on a protocol-specified interim analysis, PFS at 12 months after up to 12 cycles of therapy was significantly improved in the daratumumab group (60.7%) compared to the control group (26.9%). Patients in the daratumumab group experienced significantly better rates of ORR (82.9% versus 63.2%, $p<0.001$), ≥VGPR (59.2% versus 29.1%, $p<0.001$), and ≥CR (19.2% versus 9%, $p<0.001$).

The most frequently reported TEAEs (≥20%) in the daratumumab group were thrombocytopenia (58.8%), IRRs (45.3%), peripheral sensory neuropathy (47.3%), diarrhea (31.7%), anemia (26.3%), upper respiratory tract infection (24.7 %), fatigue (21.4%) and cough (23.9%). The most common (≥10%) ≥ Grade 3 TEAEs in the daratumumab arm were thrombocytopenia (45.3%), anemia (14.4%) and neutropenia (12.8%). Of note, the rates of ≥Grade 3 infections as well as the rates of AEs that led to treatment discontinuation were similar between the two arms of this trial.

See section 1.3 for information of other FDA approved combinations of daratumumab in NDMM: dara-VTd, dara-VMP, dara-PD, and dara-Kd.

Section 1.3 notes information of FDA approved combinations of daratumumab-SC: dara-VMP and dara-Rd, and daratumumab with bortezomib + dexamethasone.

1.3.3.3 KRd+Daratumumab in NDMM

A multi-arm phase I trial of daratumumab in combination with various regimens commonly used in NDMM is ongoing (NCT01998971). As of March 2017, 22 subjects accrued have been accrued to the KRd+daratumumab arm. The data was presented at the American Society of Clinical Oncology (ASCO) in June 2017. Based on unpublished/embargoed data available to the Sponsor-Investigator, no new safety signals have been observed to date.

1.3.4 Daratumumab Infusion-Related Reactions

Systemic reactions may occur with Dara-SC infusion. Approximately 1 in 10 patients experienced an injection related reaction. Most occurred following the first injection and were mild. 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, runny nose, fever, chest discomfort, severe itching of the skin, and hypotension.

1.3.5 Injection-Site Reactions

Localized reactions may occur at the Dara-SC injection site (injection-site reactions). In approximately 7 out of 100 patients receiving Dara-SC monotherapy, mild pain or a burning sensation was reported at the site of injection in the abdominal wall. Redness and hardening of the skin at the injection site was observed and usually disappeared within a few hours after the infusion. In general, Dara-SC infusions in the abdominal wall were well tolerated.

Injection-site reactions, all grade 1 and grade 2, were seen in (7%) patients receiving subcutaneous Daratumumab + hyaluronidase, with no treatment discontinuations. The only injection-site reaction was erythema (2%) [39]

1.4 Study Rationale and Design

Daratumumab has demonstrated clinical efficacy in relapsed and relapsed/refractory MM as monotherapy as well as in combination with dexamethasone plus either bortezomib or lenalidomide. Of note, with the exception of infusion-related reactions, neutropenia and thrombocytopenia, the safety profiles of daratumumab in combination with either bortezomib/dexamethasone or lenalidomide/dexamethasone is similar to those of the background regimens. This suggests that an anti-CD38 monoclonal antibody strategy may add to the efficacy of a given novel agent regimen without adding to its toxicity profile. There are a number of studies of daratumumab in combination with various regimens other than KRd ongoing in the NDMM population (see clinicaltrials.gov, and the daratumumab Investigator's Brochure). Further, the immunomodulatory effects of KRd have a strong potential for synergy with those of daratumumab (see Section 1.4.1).

Given the clinical activity and safety profile of daratumumab, the standard use of KRd as an induction regimen for NDMM, and the preliminary safety data from the phase I trial of KRd+daratumumab (see Section 1.3.3.3), we propose a phase II trial designed to evaluate the efficacy (rate of ≥ CR) after 8 cycles of KRd+daratumumab as induction therapy in NDMM patients (see Schema 1). The rate of ≥ CR will be compared to a historical control rate of 50% based on the studies referenced in Section 1.2.2 [8,10], with the aim of improving the rate to 70% with the addition of daratumumab. This rate would be similar to that achieved with 8 cycles of KRd+ASCT (see Section 1.2.3) [11,12]. We have incorporated identical doses of carfilzomib and lenalidomide as were used in previous trials of KRd as induction [37,38], and have maintained the weekly dose of dexamethasone as 40mg throughout induction. In the Phase I dose of KRd+daratumumab, the dose of carfilzomib was higher, at 70mg/m^2, yet no new safety signals have been reported to date (see Section 1.3.3.3). Daratumumab subcutaneously will be given at 1800mg weekly the first two cycles of induction, twice monthly cycles 3-6, and monthly cycles 7-8**.**

As outlined in Section 1.1, the typical post induction treatment course for NDMM may involve continuation of primary (induction) therapy, high dose chemotherapy +ASCT, maintenance therapy, or observation. The chosen course depends on a number of factors including response to induction, eligibility for transplant, performance status, patient preference etc. While assessment of MRD status post treatment is increasingly evaluated in clinical practice and incorporated into clinical trials, published data on its utility as a tool to select the optimal post-induction therapy are not yet available. Therefore, this trial will also allow us to gather preliminary data on use of MRD status to direct post-induction therapy. Specifically, induction will be followed by an MRD-based treatment algorithm (see Schema 2), with subjects divided into 3 separate groups:

- **Group A**: Subjects who are MRD (-) via DNA sequencing post induction will receive lenalidomide maintenance or no further treatment, at the discretion of the investigator.
- **Group B**: Subjects who remain MRD (+) via DNA sequencing post induction and are eligible for transplant will undergo ASCT. Post ASCT, those who remain MRD (+) will receive up to 12 cycles of KRd.*
- **Group C**: Subjects who remain MRD (+) via DNA sequencing post induction who are not eligible for transplant (or defer transplant) will receive up to 12 additional cycles of KRd.*

*For subjects in Group B or C, the number of cycles of KRd consolidation (maximum of 12) will depend on the MRD status during treatment. MRD status will be evaluated after completion of cycles 4, 8 and 12. Those who convert to MRD (-) via DNA sequencing after cycles 4, 8 or 12 will permanently discontinue KRd and may receive lenalidomide maintenance or no further treatment, at the discretion of the investigator. Those subjects who remain MRD (+) via DNA sequencing after 12 cycles of KRd **will** receive lenalidomide maintenance. When lenalidomide maintenance is prescribed for any subject, treatment will continue until relapse, progression, intolerance, or consent withdrawal.

All subjects will be followed until relapse or progression. Secondary endpoints in this trial include ORR, duration of response (DoR), PFS, time to disease progression (TTP), time to next

treatment (TTNT) and OS. Safety endpoints include toxicities related to daratumumab administration, other treatment associated AEs, SAEs including deaths on study treatment. A number of exploratory objectives will also be evaluated as outlined in Section 2.4, and using serial blood and bone marrow samples collected from study subjects as outlined in the Study Calendars (Section 7).

1.4.1 Correlatives

Beyond a direct anti-MM plasma cell activity, proteasome inhibitor/IMiD drug combinations such as KRd have a potent effect on immune effector cells and overall inflammation. Carfilzomib and lenalidomide in particular can activate natural killer (NK) cells and enhance NK cell-mediated lysis [18]. Bortezomib and lenalidomide have also been shown to promote Type 1 T helper (TH1) inflammation triggering T helper and cytotoxic T cells expansion [19]. Noticeably, dexamethasone can potentiate these strong pro-inflammatory stimuli by altering NK cell activating receptor expression [20] and sensitize T cells to anergy signaling [21].

The aforementioned pro-inflammatory pathways triggered by KRd present strong potential synergy with daratumumab's MM-killing mechanism and immune-modulatory effect. Antibody-dependent cellular cytotoxicity (ADCC) against CD38-positive MM cell lines has been shown after incubation with daratumumab and peripheral blood mononuclear cells (PBMCs) enriched with NK cells [22]. In addition, depletion of CD38+ regulatory cells promotes TH1 immunological events (T-helper cells and cytotoxic T-cells expansion and functionality) [23].

In the present study, in order to correlate KRd+daratumumab synergistic activity on antitumor immune function with clinical response status (MRD, ORR, PFS or OS) comprehensive peripheral immune profiling techniques will be employed throughout each line of therapy (i.e., induction, ASCT, consolidation and maintenance). These are outlined in Section 8.6.

Furthermore, changes in bone marrow microenvironment and bone marrow plasma cells (from bone marrow biopsies/aspirates performed after each line of therapy) will be investigated at the cellular and molecular level. These are also outlined in Section 8.6.2.

2. OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the efficacy of daratumumab when combined with KRd as induction chemotherapy, in terms of complete response or better, in subjects with newly diagnosed multiple myeloma.

2.2 Secondary Objectives

Secondary objectives include evaluation of daratumumab in combination with KRd by estimating Progression-free survival (PFS), Overall survival (OS), Time to disease progression (TTP), Overall response rate (ORR), Duration of response (DoR) and Time to next treatment (TTNT).

2.3 Safety Objectives

The safety objectives will include evaluation of study drug administration, adverse events assessed by NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03, serious adverse events including deaths on study treatment.

2.4 Exploratory Objectives

- Explore PET/CT response as an imaging correlate endpoint.
- Explore stem cell yield after KRd-dara induction
- Explore minimal residual disease (MRD) by:
    - Euro-flow criteria
    - DNA-PCR (Adaptive Technologies)
- Explore correlation of systemic immune profiling with measurements of clinical response such as MRD, ORR, PFS and OS by performing:
    - Cytokine profiling by multiplex protein assay
    - Blood immunotyping [including NK, NK-T and T cell subsets distribution and activation analyses] by flow cytometry
- Explore correlation of circulating T cell receptor (TCR) repertoire immuno-sequencing by NGS with parameters of clinical response such as MRD, ORR, PFS and OS.
- Examine changes in biology of BM and BM plasma cells before and after treatment(s) by B cell receptor (BCR) sequencing and global gene expression profiling
- Evaluate efficacy outcomes and safety data as a function of post-induction MRD status

3. SUBJECT SELECTION

3.1 Subject Recruitment

Subjects will be recruited at Levine Cancer Institute (LCI) locations and possibly at other participating sites.

Because no dosing or adverse event data are currently available on the use of daratumumab in combination with KRd in subjects <18 years of age, children are excluded from this study. In addition, MM is not a disease typically diagnosed in those <18 years of age.

3.2 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information signed by the subject or his/her legally authorized representative. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 (see Appendix A, Section 18.1) within 28 days prior to day 1 of treatment.

4. Confirmation of newly diagnosed multiple myeloma (NDMM) as per the IMWG 2014 criteria (see Appendix D, Section 18.4). Newly diagnosed MM patients who may have deferred transplant are also allowed.

5. Measurable disease present at baseline assessments. Baseline disease assessments are defined as disease assessments collected within 28 days of initiation of the first pre-study induction chemotherapy cycle (subjects who received prior therapy) or within 28 days prior to day 1 of study treatment (subjects with no prior therapy). Measurable disease is defined as:
    a. Serum M-protein ≥1 g/dL (≥ 0.5 g/dL for IgA or IgM) **OR**
    b. Urine M-protein ≥200 mg/24 h **OR**
    c. Involved free light chain (FLC) level ≥10 mg/dL provided serum FLC ratio is abnormal

6. No more than one prior cycle of systemic chemotherapy for MM (to accommodate subjects who needed emergent therapy at diagnosis); any prior radiotherapy must be completed at least 14 days prior to day 1 of study treatment. No more than 6 weeks should occur between completing the pre-study cycle of systemic chemotherapy and C1D1 of study treatment. It is acceptable for subjects to receive the pre-study cycle during study screening as long as subjects have recovered from treatment-induced toxicities to ≤grade 1 or baseline prior to C1D1.

7. Demonstrate adequate organ function within 1 week of day 1 of treatment as defined in the table below:

System	Laboratory Value
Hematological	
White Blood Cell (WBC)	≥ 2,000/mm^3
Absolute Neutrophil Count (ANC)	≥ 1,000/mm^3 without growth factors within 1 week of day 1 of treatment
Hemoglobin (Hgb)	≥ 8 g/dL
Platelet count	≥ 70,000/mm^3 if bone marrow plasmacytosis of <50%; otherwise ≥ 50,000/mm^3
Renal	
Creatinine clearance	creatinine clearance≥ 30 mL/min as measured by a 24-hour urine collection, or estimated by the Cockcroft – Gault formula[1]
Hepatic	
Bilirubin	≤2 × ULN; < 3.0 for subjects with Gilbert's Syndrome
Aspartate aminotransferase (AST)	≤ 3× ULN
Alanine aminotransferase (ALT)	≤ 3 × ULN
[1]See formula in Appendix B, Section 18.2	

8. Adequate cardiac function as defined by ≥45% Left Ventricular Ejection Fraction (LVEF) by ECHO or MUGA

9. Females of childbearing potential (FCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to day 1 of treatment and be willing to undergo serial serum or urine pregnancy testing. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are postmenopausal (at least 12 consecutive months with no menses without an alternative medical cause).

10. FCBP must be willing to use a highly effective contraceptive method (i.e., achieves a failure rate of <1% per year when used consistently and correctly) plus a second contraceptive method (considered acceptable [failure rate of >1% per year] or highly effective) from the time of informed consent until 3 months after the last protocol prescribed therapy (which also includes FCBP on carfilzomib) has been discontinued. **NOTE: estrogens may further increase the risk of thrombosis (beyond that associated with lenalidomide) and their use should be based on a benefit-risk decision**. For the highly effective contraceptive method, a method with low user dependency is preferable but not required (see tables, adapted from: 2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf

Highly Effective Birth Control Methods

• combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  ○ oral
  ○ intravaginal
  ○ transdermal

• progestogen-only hormonal contraception associated with inhibition of ovulation
  ○ oral
  ○ injectable
  ○ implantable[2]

• intrauterine device (IUD) [2]
• intrauterine hormone-releasing system (IUS) [2]
• vasectomised partner [2,3]
• sexual abstinence [4]
[1] Hormonal contraception may be susceptible to interaction with the investigational medicinal product (IMP), which may reduce the efficacy of the contraception method [2] Contraception methods that in the context of this guidance are considered to have low user dependency. [3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success. [4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Acceptable Birth Control Methods
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide[1]
• Cap, diaphragm or sponge with spermicide[1]
[1]A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

11. Male subjects (even those who have had a vasectomy) who are sexually active with a FCBP must be willing to use latex or synthetic condoms from initiation of study treatment until 3 months after the last protocol prescribed therapy has been discontinued. They must also refrain from donating sperm for at least 90 days after the last dose of carfilzomib and at least 90 days from the last dose of daratumumab. The FCBP partner should also consider contraception recommendations (see inclusion #10).

12. As determined by the enrolling physician, ability of the subject to understand and comply with study procedures for the entire length of the study.

3.3 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Any infection requiring systemic therapy (i.e. involving IV antibiotics) (**NOTE:** at discretion of investigator, subjects with uncomplicated urinary tract infections may be eligible).

2. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study, and any female subject must agree not to donate eggs during the study and for 3 months after the last protocol prescribed therapy has been discontinued).

3. Known previous or concurrent malignancies in the last two years other than multiple myeloma are excluded. The only allowed exceptions are:
   - Adequately treated non-invasive bladder cancer that is considered cured
   - Adequately treated skin cancer (non-melanoma or melanoma) that is considered cured
   - Adequately treated non-invasive cervical cancer that is considered cured
   - Adequately treated localized prostate cancer considered to have a very low risk of recurrence
   - Adequately treated lobular carcinoma in situ, ductal carcinoma in situ, or localized breast cancer considered to have a very low risk of recurrence
   - Other malignancy that is considered cured with minimal risk of recurrence from which the patient has been disease free for at least 2 years
   - The participant must not be receiving active therapy, other than hormonal therapy for other malignancy

4. Non-secretory MM.

5. Active involvement of the central nervous system by MM.

6. Prior cardiovascular cerebrovascular accident with persistent neurological deficit.

7. Has chronic obstructive pulmonary disease with a forced expiratory volume in 1 second (FEV1) < 50% of predicted normal. FEV1 is required for subjects suspected of having chronic obstructive pulmonary disease and are not eligible if FEV1 is < 50% of predicted normal.

8. Has had moderate or severe persistent asthma within the past 2 years from enrollment and/or has currently uncontrolled asthma of any classification, as defined by the National Asthma Education and Prevention Program/NIH (see Appendix 18.5 and 18.6). Note that participants who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate.

9. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

10. Had major surgery within 2 weeks prior to day 1 of treatment. Kyphoplasty is not considered major surgery.

11. Exposure to any investigational drug (including investigational vaccine) or invasive investigational medical device within 4 weeks or 5 pharmacokinetic half-lives prior to day 1 of treatment, whichever is longer.

12. Uncontrolled clinically significant illness including, but not limited to, uncontrolled hypertension (as per the most updated Joint National Committee for the Management of Hypertension definitions), symptomatic congestive heart failure (as per New York Heart Association [NYHA] class III or IV [see Appendix C, Section 18.3], uncontrolled angina pectoris, myocardial infarction within the past 6 months from consent, known or suspected amyloidosis, uncontrolled cardiac arrhythmia, psychiatric illness/social situations that would limit compliance with study requirements as determined by the investigator, or any other condition (including laboratory abnormalities) that would, in the opinion of the investigator, place the subject at unacceptable risk if he/she were to participate in the study.

13. Known allergies, hypersensitivity or intolerance to monoclonal antibodies or human proteins, daratumumab+hyaluronidase or its excipients or known sensitivity to mammalian-derived products, carfilzomib or its excipients, lenalidomide or its excipients, or dexamethasone or its excipients.

14. Is 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 HBV vaccination, do not need to be tested for HBV DNA by PCR.

15. Is known to be 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). Subject is not required to have hepatitis C testing at screening.

16. Is known to be seropositive for human immunodeficiency virus.

17. Transplant ineligible subjects > 70 years old only: Defined frail, per IMWG criteria of 'frailty' [32]. Frailty assessment does not need to be performed unless the subject is transplant ineligible and > 70 years old. "Frail" is defined as a frailty score of ≥ 2.

18. Prior or current exposure to daratumumab or other anti-CD-38 therapies.
    - Prior or current exposure to daratumumab will be allowed if administered with a pre-study cycle of induction chemotherapy that consists of carfilzomib, lenalidomide and dexamethasone OR bortezomib, lenalidomide and dexamethasone.
    - Prior or current exposure to daratumumab must be in accordance with Section 3.2, Inclusion #6: No more than one prior cycle of systemic therapy (completed within 6 weeks of consent) for MM (to accommodate subjects who needed emergent therapy at diagnosis); any prior radiotherapy must be completed at least 14 days prior to day 1 of treatment. Subject must have recovered from treatment-induced toxicities to ≤grade 1 or baseline.

19. Focal radiation therapy within 14 days prior to C1D1 with the exception of palliative radiotherapy for symptomatic management but not on measurable extramedullary plasmacytoma.

3.4 Screen Failures

A subject who, for any reason (e.g. failure to satisfy the selection criteria or withdraws consent), terminates his/her study participation before receiving the first dose of study treatment is regarded as a "screen failure." All screen failures will be tracked. Reason (e.g. specific inclusion/exclusion criteria) for screen failure will be recorded in the CTMS. Enrollment will continue until the targeted sample size in the evaluable population (Section 14.4) is achieved.

4. REGISTRATION

Following informed consent, subjects will be registered by the Coordinating Center and assigned a Sequence Number. A subject is considered registered when they are assigned a Sequence Number.

5. STUDY PLAN

See Schema 1 and Schema 2.

This single arm, two-stage, open-label Phase II study is designed with the primary objective of evaluating the efficacy of induction therapy comprised of 8 cycles of carfilzomib, lenalidomide, dexamethasone and daratumumab (KRd+daratumumab) in terms of complete response or better in subjects with NDMM and comparing to relevant historical controls. After induction, all subjects will undergo disease evaluation. Those who experience ≥VGPR will undergo an assessment of minimal residual disease (MRD) and will be classified as MRD (+) or MRD (-) as determined by MRD via DNA sequencing. (**NOTE:** MRD will be evaluated via flow cytometry and DNA sequencing. If MRD via DNA sequencing detects MRD, the subject will be classified as MRD (+)). Those with <VGPR will be considered to have MRD (+) disease and will follow MRD (+) algorithm. Based on MRD DNA sequencing results, subjects will be divided into 3 separate treatment groups (see Schema 2). All treatment decisions will be based from MRD via DNA sequencing results. Subsequent MRD assessments (as outlined in Schema 2) will follow the same paradigm described above for the post-induction disease assessment. All subjects in each group will be followed until relapse or progression.

For subjects who completed a pre-study cycle of induction chemotherapy containing daratumumab and/or carfilzomib, only 7 cycles of KRdD Induction should be given.

All subjects considered eligible for transplant (as per institutional standards based on age, medical history, overall health, co-morbid conditions, physical examination and laboratory studies) will undergo stem cell mobilization and collection any time after Cycle 3 of induction. Given difficulties with stem cell mobilization later during KRD-dara induction, initial attempt at stem cell collection is preferred after C3 or C4 of induction. (per investigator discretion; see Section 5.2 and Induction Calendar Section 7.1).

This study will initially open as a single center study at LCI and additional investigational site(s) may be added following activation at the coordinating center. We anticipate subjects will be accrued over 24 months.

5.1 KRd+Daratumumab Induction Regimen

All subjects enrolled will receive KRd+daratumumab induction. See Section 6 for details on drug administration and dose modifications/delays.

5.1.1 Table 1: Overview of KRd+Daratumumab Induction Regimen (Daratumumab SC)

Drug	Dose	Route	Schedule	4-Week (28D) Cycle
Carfilzomib[a,b]	20 mg/m^2	IV	D1	Cycle 1▲
Carfilzomib[a,b]	56 mg/m^2	IV	D 8, 15	Cycle 1▲
Carfilzomib[a,b]	56 mg/m^2	IV	D1, 8, 15	Cycles 2-8*
Lenalidomide[c]	25 mg	Oral	Once a day on D1-21	Cycles 1-8*
Dexamethasone[d]	40 mg	Oral/IV	Once weekly on D1, 8, 15, 22	Cycles 1-8*
Daratumumab	1800 mg	SC	D1, 8, 15, 22	Cycles 1-2▲
Daratumumab	1800 mg	SC	Twice Monthly on D1, D15	Cycles 3-6▲
Daratumumab	1800 mg	SC	Once monthly on D1	Cycles 7-8*▲

[a] Calculate the dose using the subject's actual body surface area (BSA) at baseline (the most recent weight collected prior to study treatment on C1D1). For subjects with a BSA >2.2m^2, calculate the dose based upon a BSA of 2.2m^2. **NOTE:** Use the subject's actual (not ideal) body weight for dosing as per the American Society of Clinical Oncology (ASCO) guidelines on dosing of obese adult subjects. If a subject's weight changes by more than 20% from cycle 1 day 1 the dose of carfilzomib should be recalculated.

[b] **NOTE**: In subjects who enroll with a bilirubin and/or AST >1 x ULN, the starting dose of carfilzomib should be reduced by 25% to 42 mg/m^2 (maintain the first dose of 20mg/m^2). The dose may be escalated to 56mg/m^2 if both bilirubin and AST resolve to ≤ ULN.

[c] For subjects who enroll with a CrCl between 30-50 mL/min, the starting dose of lenalidomide may be reduced to 10mg

[d] At discretion of the investigator, dexamethasone may be given as 20mg over 2 consecutive days each week. Additionally, dexamethasone may be given at 20 mg once weekly for subjects >75 years old, diabetic subjects, and underweight subjects.

▲For subjects who received daratumumab and/or carfilzomib as part of a cycle of pre-study induction chemotherapy, this should be considered Cycle 1 of daratumumab and /or carfilzomib, and they should enter the study as Cycle 1, but receiving the standard Cycle 2 schedule of daratumumab and/or carfilzomib.

(For example:

- **If subject receives daratumumab without carfilzomib in a pre-study cycle, the subject will enter the study on Cycle 1 with the Cycle 2 *schedule of daratumumab dosing* and will receive carfilzomib with Cycle 1 *schedule of carfilzomib dosing* during their on-study Cycle 1.**
- **If a subject receives carfilzomib without daratumumab in a pre-study cycle, the subject will enter the study on Cycle 1 with the Cycle 2 *schedule of carfilzomib dosing* and will receive daratumumab with the Cycle 1 *schedule of daratumumab dosing* during their on-study Cycle 1.**
- **If a subject received both daratumumab and carfilzomib in a pre-study cycle, the subject will enter the study on Cycle 1 with the Cycle 2 *schedule of dosing* for both daratumumab and carfilzomib during their on-study Cycle 1.)**

***NOTE: For subjects who completed a pre-study cycle of induction chemotherapy, only 7 cycles of KRdD Induction should be given.**

5.2 Stem Cell Mobilization and Collection

All subjects who are considered eligible for transplant at the discretion of the investigator (and as per institutional standards based on age, medical history, overall health, co-morbid conditions, physical examination and laboratory studies) will undergo stem cell mobilization and collection,

any time after Cycle 3 of induction. Given difficulties with stem cell mobilization later during KRD-dara induction, initial attempt at stem cell collection is preferred after C3 or C4 of induction. This will be completed with the hematopoietic growth factor G-CSF (filgrastim or equivalent) with or without the chemokine receptor type 4 (CXCR4) antagonist plerixafor, as per institutional standards. Collection and freezing of stem cells should be performed as per institutional standards. For subjects who fail collection of adequate stem cells during induction or post-induction, re-attempts at mobilization and stem cell collection are acceptable during maintenance therapy per investigator discretion. Treatment can be held during mobilization/ collection per investigator discretion, and it will not be considered a protocol deviation.

AEs related to mobilization do not need to be reported. However, any AEs considered related to induction (i.e., either daratumumab, carfilzomib, lenalidomide and/or dexamethasone) should continue to be reported.

5.3 MRD Based Treatment Algorithm

After completion of 8 cycles of induction, those subjects who experience ≥VGPR will undergo an assessment of MRD by flow cytometry and DNA sequencing and will be classified as MRD (+) or MRD (-) as determined by MRD via DNA sequencing. Those with <VGPR will be considered to have MRD (+) disease. Results of MRD testing via DNA sequencing will be used to separate subjects into **Group A** [MRD (-)], **Group B** [MRD (+) and eligible for transplant] and **Group C** [MRD (+) and NOT eligible (or defer) for transplant]. If a subject does not have an NGS MRD **test report** available (for whatever reason), the subject will be assumed to be MRD + and will receive treatment as though MRD+ per the algorithm. Subjects who do not have an adequate baseline NGS MRD **sample** (for whatever reason) will be considered MRD unevaluable and will receive treatment as though MRD + for all subsequent MRD time-points. Also, all subsequent protocol directed NGS MRD samples do not need to be collected for these subjects. **NOTE**: The 10^{-5} MRD result from the NGS MRD test will be used for treatment decisions.

5.3.1 Group A

Subjects who are MRD (-) post induction via DNA sequencing may receive lenalidomide maintenance (as per Section 5.6) until relapse or progression or no further treatment, at the discretion of the investigator. If prescribed in transplant eligible subjects, lenalidomide maintenance therapy may begin after recovery from stem cell mobilization and collection.

5.3.2 Group B

Subjects who are MRD (+) via DNA sequencing and eligible for transplant will undergo high dose chemotherapy (HDC) and ASCT (as per Section 5.4), followed by a second MRD evaluation. Results of the second MRD testing via DNA sequencing will be used to determine subsequent treatment: any Group B subject who converts to MRD (-) disease via DNA sequencing after ASCT may receive lenalidomide maintenance (as per Section 5.6) until relapse or progression or no further treatment, at the discretion of the investigator; any Group B subject who is MRD (+) via DNA sequencing after ASCT will receive up to 12 cycles of KRd consolidation (as per Section 5.5). The number of cycles will depend on the MRD status via DNA sequencing during treatment. MRD status will be evaluated after completion of cycles 4, 8 and 12. Any subject who converts to MRD (-) via DNA sequencing disease after 4, 8 or 12

cycles of KRd consolidation will permanently discontinue KRd and may receive lenalidomide maintenance (as per Section 5.6) until relapse or progression or no further treatment, at the discretion of the investigator. Those who have MRD (+) disease via DNA sequencing after 12 cycles of KRd consolidation **will** receive lenalidomide maintenance until relapse or progression (as per Section 5.6).

5.3.3 Group C

Subjects who are MRD (+) via DNA sequencing and NOT eligible for or defer transplant will receive up to 12 cycles of KRd consolidation (as per Section 5.5). The number of cycles will depend on the MRD status via DNA sequencing during treatment. MRD status will be evaluated after completion of cycles 4, 8 and 12.

Any subject who converts to MRD (-) disease via DNA sequencing after 4, 8 or 12 cycles of KRd consolidation will permanently discontinue KRd and may receive lenalidomide maintenance (as per Section 5.6) until relapse or progression or no further treatment, at the discretion of the investigator. Those who have MRD (+) disease via DNA sequencing after 12 cycles of KRd consolidation **will** receive lenalidomide maintenance until relapse or progression (as per Section 5.6).

5.4 ASCT for Group B

After recovery from stem cell mobilization and collection, HDT (melphalan) should be administered followed by ASCT, as per institutional standards, including any necessary prophylactic antibiotics, hematopoietic growth factors, and other supportive care during and post ASCT. AEs related to HDC and ASCT do not need to be reported. However, any AEs considered related to induction (i.e., either daratumumab, carfilzomib, lenalidomide and/or dexamethasone) should continue to be reported.

Disease evaluation after ASCT will take place after engraftment is complete, as defined per institutional standards. Subsequent treatment can be initiated at the discretion of the investigator after disease evaluation and recovery from ASCT (~60-100 days post ASCT).

5.5 KRd Regimen for Consolidation (Groups B and C)

Table 2: Overview of KRd Regimen for Consolidation

Drug	Dose	Route	Schedule	4-Week (28D) Cycle
Carfilzomib[a]	56 mg/m^2 or LTD[b]	IV over approximately 30 minutes	On days D1, 8, 15	Cycles 1-12[d]
Lenalidomide	10-15 mg[c]	Oral	Once a day on D1-21	Cycles 1-12[d]
Dexamethasone	20 mg or LTD[b]	Oral/IV	Once every 2 weeks on D1,15	Cycles 1-12[d]

[a]Calculate the dose using the subject's actual body surface area (BSA) at baseline (baseline weight in consolidation is defined as the most recent weight prior to initiation of C1D1 of consolidation). For subjects with a BSA >2.2m^2, calculate the dose based upon a BSA of 2.2m^2. If a subject's weight changes by more than 20% from cycle 1 day 1 of consolidation the dose of carfilzomib should be recalculated. **NOTE:** Use the subject's actual (not ideal) body weight for dosing as per the American Society of Clinical Oncology (ASCO) guidelines on dosing of obese adult subjects.
[b]LTD= last tolerated dose from end of induction
[c]10 or 15 mg orally at discretion of investigator
[d] Subjects will receive up to 12 cycles, depending on MRD status via DNA sequencing during treatment, see Sections 5.3.2 and 5.3.3.

5.6 Lenalidomide Maintenance

Revlimid is currently FDA approved for maintenance in patients following a stem cell transplant until disease progression and in patients who do not receive a stem cell transplant irrespective of depth of response. The role of stopping treatment for MRD negative patients is investigational.

Table 3: Lenalidomide Maintenance

Drug	Dose	Route	Schedule	4-Week (28D) Cycle
Lenalidomide	10 mg or LTD[a]	Oral	Once a day on D1-21	Until relapse or progression
[a]LTD= last tolerated dose (if <10 mg)				

For subjects receiving lenalidomide for maintenance, creatinine clearance should be reviewed, and dosing followed per Section 6.3.2.2.

6. TREATMENT DETAILS AND DOSE MODIFICATIONS/DELAYS

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each subject will be assessed periodically for the development of any toxicity according to the Study Calendars. Toxicity will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

In the event of a possible drug-related toxicity, the investigator should, to the best of his/her ability, assess its relationship to each of the drugs within the regimen when KRd + daratumumab, or KRd are prescribed, or to the combination to the extent possible. Actions outlined in the sections below should be instituted for the agent(s) considered likely to be involved. Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor-Investigator; unless required for immediate subject safety. **NOTE:** if any agent(s) in the regimen is discontinued, treatment should continue with the remaining agent(s).

If dosing is delayed during a cycle (for any reason), any doses not administered will not be made up (i.e., the length of the cycle should be maintained).

6.1 Carfilzomib

6.1.1 Administration

If a subject's weight changes by more than 20% from induction C1D1 (or KRd consolidation C1D1), the subject's BSA and carfilzomib dose should be recalculated. Carfilzomib should be administered only after the dose is diluted in 5% Dextrose Injection, USP.

Pre-medications for carfilzomib should be included per investigator discretion. Subjects will receive carfilzomib as an intravenous (IV) infusion over approximately 30 minutes as per the dose and schedule outlined in Table 1 for induction, and/or in Table 2 for consolidation. If the subject 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. The dose must be administered at a facility capable of managing IRRs.

On the days both carfilzomib and daratumumab are due to be administered, carfilzomib will be administered first.

6.1.2 Pre- and Post-Dose Hydration and Monitoring for Carfilzomib

IV hydration will be given immediately prior to carfilzomib per investigator discretion. This will consist of normal saline or other appropriate IV fluid, the volume to be determined per investigator discretion. Subject should remain in clinic for at least 1 hour observation period for the first dose on study, and per investigator discretion for subsequent doses. During this period, post dose IV hydration (normal saline or other appropriate IV fluid formulation) will be given, per investigator discretion. Subjects should be monitored periodically during this period for evidence of fluid overload.

If lactate dehydrogenase (LDH) or uric acid is elevated (and/or in subjects considered still at risk for TLS) after the second dose in Cycle 1 of induction, then the recommended IV hydration should be given additionally before each remaining dose per investigator discretion. The goal of the hydration program is to maintain robust urine output (e.g. $\geq$ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.

6.1.3 First Dose Effect for Carfilzomib during Induction

A "first dose effect" has been seen with carfilzomib, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release. Should a "first dose" effect occur at any point during Cycle 1 or 2 of induction, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available and instituted, as medically indicated.

6.1.4 Dose Modifications for Carfilzomib-Related Toxicities

If a dose of carfilzomib is missed, the subject should not be administered an additional dose, but should be given the next usual prescribed dose.

Refer to the following table for carfilzomib dose levels when dose reductions are required during induction:

Table 4: Dose Levels for Carfilzomib during Induction

Dose Level	Dose	Schedule
0*	56 mg/m^2	D1, 8, 15
- 1	45 mg/m^2	D1, 8, 15
- 2	36 mg/m^2	D1, 8, 15
- 3	27 mg/m^2	D1, 8, 15
-4	20 mg/m^2	D1, 8, 15

* Dose level 0 refers to the starting dose for carfilzomib during Induction

Refer to the following table for carfilzomib dose levels when dose reductions are required during consolidation:

Table 5: Dose Levels for Carfilzomib during Consolidation

Dose Level	Dose	Schedule
0*	56 mg/m^2	D1, 8, 15
- 1	45 mg/m^2	D1, 8, 15
- 2	36 mg/m^2	D1, 8, 15
-3	27 mg/m^2	D1, 8, 15
-4	20 mg/m^2	D1, 8, 15

* Dose level 0 refers to the starting dose for carfilzomib during Consolidation

If dose reductions of carfilzomib beyond those levels listed in Tables 4 and 5, this agent should be permanently discontinued.

6.1.4.1 Carfilzomib Hematologic Toxicities

NOTE: Thrombocytopenia has been transient and typically resolves during the week between treatments.

Table 6: Carfilzomib Dose Modifications for Hematologic Toxicities

Toxicity	Recommended Action
ANC < 500/mm^3	• For first occurrence: hold dose; resume at same dose level once ANC recovers to ≥ 500/mm^3 • For subsequent occurrence(s), hold dose; resume with dose reduced by 1 level once ANC recovers to ≥ 500/mm^3
ANC < 500/mm^3 and temperature >38.5ºC or 2 consecutive readings of >38.0ºC for 2 hours	• Hold dose; resume at same dose level once ANC returns to baseline and fever resolves
Platelets < 10,000/mm^3 or evidence of bleeding with thrombocytopenia	• First occurrence: hold dose; resume at same dose level once platelets recover to ≥ 10,000/mm^3 and/or bleeding is controlled • For subsequent occurrence(s), hold dose; resume with dose reduced by 1 level once platelets recover to ≥ 10,000/mm^3 and/or bleeding is controlled

6.1.4.2 Carfilzomib Non-Hematologic Toxicities

Creatinine clearance (CrCl) changes associated with carfilzomib are mostly transient, reversible, and non-cumulative. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib on Day 1, 8, and 15 of Cycles 1 and 2 during induction, and on Day 1 and 15 of Cycles 3-8 of induction and all consolidation cycles. Creatinine clearance should be calculated on Day 1 of each cycle.

Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered as clinically indicated to prevent dehydration.

Subjects with active or suspected infection of any kind that require systemic treatment should not be dosed with carfilzomib until the infection has resolved and if being treated with an anti-infective(s), the course of antibiotics has been completed.

Subjects with a history of HBV should be closely monitored for signs and symptoms of active HBV infection throughout treatment with carfilzomib, including the 30-day safety monitoring follow-up period.

Subjects receiving carfilzomib should be monitored for any new or worsening neurologic, cognitive or behavioral signs and symptoms that may be suggestive of Progressive Multifocal Leukoencephalopathy (PML) as part of the differential diagnosis of central nervous system disorders. If PML is suspected, carfilzomib should be held and subjects referred to a specialist and appropriate diagnostic testing should be initiated. If a PML diagnosis is confirmed, carfilzomib should be permanently discontinued.

Table 7: Carfilzomib Dose Modifications for Non-Hematologic Toxicities

Toxicity	Recommended Action
Serum creatinine ≥ 2 X baseline or CrCl < 15mL/min, or CrCl decreases to ≤ 50% of baseline, or need for hemodialysis (Creatinine clearance only applicable for Day 1 of each cycle)	• Hold dose and continue monitoring renal function • If attributable to carfilzomib, resume with dose reduced by 1 level once renal function has recovered to within 25% of baseline • If not attributable to carfilzomib, dosing may be resumed at discretion of investigator • If on hemodialysis, administer the dose after the hemodialysis procedure
Grade 2 elevation in total bilirubin or AST and/or ALT	• Reduce 1 dose level • Dose may be re-escalated if LFT return to normal or baseline level and DILI* is excluded
Grade ≥ 3 elevation in total bilirubin or AST and/or ALT	• Hold dose; resume with dose reduced by 1 level once LFT return to normal or baseline level and DILI* is excluded
DILI* attributed to carfilzomib ***DILI:** clinician has reviewed case and 1) established that event is not transient elevation of transaminases (there is evidence of hepatic synthetic dysfunction e.g. coagulopathy) and 2) clinician has considered a differential diagnosis, investigated for other potential causes (e.g. reactivation of viral hepatitis, sepsis, auto-immune, or other common drug causes) and, has concluded that there has been a liver injury and that carfilzomib was the cause*	• Discontinue carfilzomib
If Posterior Reversible Encephalopathy Syndrome (PRES) is suspected	• Hold dose; consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. • If confirmed, permanently discontinue carfilzomib • If the diagnosis of PRES is excluded and if clinically appropriate, restart dose administration • If PRES recurs, permanently discontinue carfilzomib
If thrombotic microangiopathy (TMA) (TTP/HUS) is suspected	• Hold dose; and manage per standard of care including plasma exchange as clinically appropriate • If TMA is confirmed and related to carfilzomib, permanently discontinue • If diagnosis is excluded, carfilzomib can be re started at the previous dose • If the condition recurs, permanently discontinue carfilzomib

Hypertensive Urgency/emergency (defined as sustained or persistent SBO ≥ 180 mmHg or DBP ≥ 110mmHg)	• Hold dose until resolution to baseline and restart at 1 dose decrement
If Progressive Multifocal Leukoencephalopathy (PML) is suspected	• HOLD carfilzomib administration and refer to a specialist; appropriate diagnostic testing should be initiated • If the diagnosis of PML is confirmed, permanently discontinue carfilzomib
Active HBV reactivation	• Withhold carfilzomib until the infection is adequately controlled. If the benefits outweigh the risks, carfilzomib may be resumed with concomitant prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.
Active or suspected infection of any kind that requires systemic treatment	• Hold carfilzomib until the infection has resolved and the course of antibiotics has been completed, if being treated with an anti-infective(s)
≥ Grade 3 non-hematologic toxicity[a]	• Hold dose; resume with dose reduced by 1 level once resolved or returned to baseline
[a]Other than nausea, vomiting or diarrhea that responds to supportive care within 7 days, or Grade 3 fatigue or asthenia that lasts <7 days	

6.2 Daratumumab

6.2.1 Administration

For Cycle 1 Day 1 of induction, daratumumab dose should be administered only after the observation period post carfilzomib is complete. Daratumumab will be administered by subcutaneous (SC) injection. See Study Calendar for Induction regarding "blood type and screen" requirements of all subjects prior to the first dose.

Daratumumab-SC will be provided as a fixed-dose (1800 mg), combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.

See Sections 1.3.4 and 10.1.7, and the most up to date prescribing information and Investigator's Brochure for details on IRRs from daratumumab. To reduce the risk of reactions during the infusion, subjects should be pre-medicated as outlined in Section 6.2.2. Each daratumumab dose must be administered at a facility capable of managing infusion-related reactions. See section 6.2.5 for management of any daratumumab infusion-related reaction.

Daratumumab (1800 mg) will be administered by SC injection by manual push over approximately 3 – 5 minutes in the abdominal subcutaneous tissues in the left/right locations, alternating between individual doses. The volume of the SC solution will be 15 mL for the 1800 mg dose. If the subject experiences pain during the administration, the injection should be paused

or slowed. If pausing or slowing the delivery rate does not alleviate the pain, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

Subject should remain in clinic for at least 1 hour observation period for the first dose on study, and per investigator discretion for subsequent doses. Reasons for continued observation on subsequent daratumumab infusion may include but are not limited to the following: subjects with a higher risk of respiratory complications (e.g., subjects with mild asthma or subjects with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history), subjects who experience infusion-related reactions with the first injection of study drug, subject with decreased condition on day of dosing compared to prior dosing day. The dose of daratumumab will remain constant throughout the study.

Vital signs should be measured during Induction per institutional standards but at a minimum before the start of injection for all doses. Measurement of vital signs at the end of the injection is only required for C1D1 and C1D8 and thereafter per investigator discretion. If the subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation. If the subject has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as an SAE.

6.2.2 Pre-Daratumumab Medications

Cycle 1 of Induction
On Cycle 1 Day 1 dexamethasone administered as protocol-directed therapy per Section 6.4 will be administered at a dose of 40 mg or as 20 mg over 2 doses per investigator discretion and will also serve as daratumumab pre-medication given 1-3 hours prior to the daratumumab dose.

All cycles
All pre- and post- dosing medications to be administered per institutional standards.
Dexamethasone administered as protocol-directed therapy per Section 6.4 will also serve as daratumumab pre-medication given oral/IV 1-3 hours prior to daratumumab dose.

NOTE: Subjects with a history of chronic obstructive pulmonary disease (COPD) may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for subjects with COPD.

The following are ***recommended*** guidelines for prevention and management of infusion reactions, but ***can be adjusted per investigator***:
All participants will receive the following medications 1 to 3 hours prior to each study drug administration:

- An antipyretic: paracetamol (acetaminophen) 650-1000 mg IV or PO
- An antihistamine: diphenhydramine 25-50 mg IV or PO or equivalent. Avoid IV use of promethazine.

  - After Cycle 6, if a participant has not developed an infusion-related reaction and is intolerant to antihistamines, modifications are acceptable as per investigator discretion.
- Corticosteroids (Long-acting or intermediate-acting):
  - *Monotherapy:* Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg or equivalent).
  - *Combination therapy:*
    - Administer 20 mg dexamethasone (or equivalent) prior to every daratumumab infusion. When dexamethasone is the background regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on daratumumab infusion days.
    - Dexamethasone is given orally or intravenously prior to the first daratumumab infusion and oral administration may be considered prior to subsequent infusions.
  - If the subject does not experience a major systemic administration-related reaction after the first 3 doses, consider discontinuing the administration of corticosteroids (excluding any background regimen-specific corticosteroid).

Pre-dose administration of a leukotriene inhibitor (montelukast 10 mg PO or equivalent) is optional in Cycle 1 Day 1 and can be administered up to 24 hours before infusion as per investigator discretion.

If necessary, all PO pre-infusion medications may be administered out of the clinic on the day of the infusion, provided they are taken within 3 hours before the infusion.

6.2.3 Post-Daratumumab Medications

Cycle 1 of Induction

Cycle 1 (D1 and D8 only), the subject should take 4mg of dexamethasone orally 24 and 48 hours post daratumumab. **NOTE**: if the 40 mg dose of dexamethasone as part of the KRd regimen is given as 20mg over 2 days, the 24-hour 4 mg dose of dexamethasone can be omitted.

The following are ***recommended*** guidelines to reduce the risk of delayed infusion related reactions, but ***can be adjusted per investigator***:

- *Monotherapy studies:*
  - In an effort to prevent delayed infusion-related reactions, all participants will receive long- or intermediate-acting corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following all daratumumab infusions (beginning the day after the infusion).
  - In the absence of infusion related AEs after the first 3 infusions, post-infusion corticosteroids should be administered per investigator discretion.
- *Combination therapy:*
  - Consider administering low-dose methylprednisolone (≤ 20 mg) or equivalent, the day after the infusion. However, if a background regimen-specific corticosteroid

(e.g. dexamethasone) is administered the day after the infusion, additional post-infusion steroids are not required, but may be considered by the investigator.

All cycles

Per investigator's discretion, if high risk participants are not hospitalized for monitoring, a follow-up telephone call should be made to monitor their condition within 48 hours (no later than 72 hours) after all drug administrations. If the participant has not experienced a significant medical event but is hospitalized overnight only for observation, then the hospitalization should not be reported as a serious adverse event. Investigators may prescribe bronchodilators, H1-antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after participants are released from the hospital/clinic. If an at-risk participant experiences no major infusion-related reactions, then these post-administration medications may be waived after 4 doses at the investigator's discretion.

6.2.4 Dose Delay for Daratumumab-Related Toxicities

Dose modification (increase or decrease) of daratumumab is not permitted. Dose delay is the primary method for managing daratumumab-related toxicities, as outlined in Sections 6.2.5 and 6.2.6.

Unless otherwise noted below, daratumumab treatment may be delayed ≤ 4 weeks from the expected day of the next treatment for any reason. If treatment is delayed for > 4 weeks, daratumumab will be permanently discontinued.

6.2.5 Infusion-Related Reaction (IRR) for Daratumumab SC

Infusion-related reactions (IRRs) are systemic reactions related to daratumumab administration. Participants should be observed carefully during daratumumab administrations. Trained study staff at the clinic should be prepared to intervene in case of any IRRs, and resources necessary for resuscitation (e.g., agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at the bedside. Attention to staffing should be considered when multiple participants will be dosed at the same time. If an IRR develops during Dara SC administration, then the administration should be temporarily interrupted. Participants who experience AEs during Dara-SC administration must be treated for their symptoms. Participants should be treated with paracetamol (acetaminophen), antihistamine, or corticosteroids, as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require vasopressors. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, Dara-SC should be discontinued.

Infusion-related Reactions <Grade 3:

If the investigator assesses an IRR less than (<) Grade 3 to be related to administration of study intervention, then the Dara-SC administration should be interrupted. When the participant's condition is stable, Dara-SC administration may be restarted at the investigator's discretion.

If the participant experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the participant must be permanently discontinued from Dara-SC treatment.

Infusion-related Reactions Grade 3 or Higher:
For IRR AEs (other than laryngeal edema or bronchospasm) that are Grade 3, the Dara-SC administration must be stopped, and the participant must be observed carefully until resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the Dara-SC administration may be restarted at the investigator's discretion.
If the intensity of the AE returns to Grade 3 after restart of the Dara-SC administration, then the participant must be permanently discontinued from Dara-SC treatment.
For IRR AEs that are Grade 4, the Dara-SC administration must be stopped, and the participant permanently discontinued from Dara-SC treatment.

Recurrent Infusion-related Reactions:
If a Grade 3 IRR (or Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm) recurs during or within 24 hours after a subsequent Dara-SC administration, the participant must be permanently discontinued from Dara-SC treatment.

Injection Site Reactions:
In clinical studies, SC administration of daratumumab was associated with local injection site reactions, such as induration and erythema, in some subjects. The reactions usually resolved within 60 minutes. Local injection-site reactions should be managed per institutional standards.

6.2.6 Other Daratumumab Toxicities

Hold daratumumab for the following hematologic toxicities, regardless of relationship to daratumumab:

- Grade 4 neutropenia
- ≥Grade 3 or higher thrombocytopenia with bleeding
- ≥ Grade 3 febrile neutropenia or neutropenia with infection

For other ≥ Grade 3 non-hematologic toxicities, hold daratumumab only if specifically related to daratumumab with the following exceptions:

- Grade 3 nausea that responds to antiemetic treatment within 7 days
- Grade 3 vomiting that responds to antiemetic treatment within 7 days
- Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
- Grade 3 fatigue or asthenia that lasts for <7 days after the last administration of daratumumab

Daratumumab treatment should be resumed when the toxicity has resolved to ≤ Grade 2. If the daratumumab administration does not commence within the pre-specified window (Table 8) of the scheduled administration date, then the dose will be considered a missed dose.

Administration may resume at the next planned dosing date. A missed dose will not be made up. If the daratumumab is administered within the pre-specified window, the schedule of subsequent doses of daratumumab does **NOT** need to be adjusted.

Table 8: Allowed Delays of Daratumumab Based on Schedule

Cycles	Frequency	If Dose Delay:	Dosing Resumption
1-2	Weekly	>3 days, miss dose	next planned weekly dosing date
3-6	Every 2 weeks	>14 days, miss dose	next planned dosing date
7-8	Every 4 weeks	>21 days, miss dose	next planned dosing date

6.3 Lenalidomide

6.3.1 Administration

Lenalidomide is self-administered and should be taken orally at about the same time each day with water. It may be taken on a full or empty stomach. Subjects should not break, chew or open capsules. Missed doses of lenalidomide will not be made up. If dosing with lenalidomide is delayed due to an extenuating circumstance (e.g., needing a new prescription due to dose reduction), a delay of up to 5 days will not be considered a deviation.

6.3.2 Dose Modification for Lenalidomide-Related Toxicities

If a dose of lenalidomide is missed, the subject should not take an additional dose, but should take the next usual prescribed dose.

Refer to the following table for lenalidomide dose levels when dose reductions are required during induction, consolidation or maintenance:

Table 9: Dose Levels for Lenalidomide[1]

Dose Level	Dose	Schedule
0[2]	25 mg	D1-21
- 1	15mg	D1-21
- 2	10mg	D1-21
- 3	5mg	D1-21
- 4	2.5mg	D1-21
- 5	2.5mg	Every other day during D1-21

[1]If dose reduction required due to renal dysfunction, see Section 6.3.2.2, Table 11.

[2] Dose level 0 refers to the starting dose of lenalidomide during Induction

6.3.2.1 Lenalidomide Hematologic Toxicities

Table 10a: Lenalidomide Dose Modifications for Hematologic Toxicities

Toxicity	Recommended Action
ANC < 1000/mm^3	• Interrupt lenalidomide • Resume at same dose level once ANC recovers to ≥ 1000/mm^3 • For any recurrence, interrupt lenalidomide; resume with dose reduced by 1 level once ANC recovers to ≥ 1000/mm^3
Platelets < 30,000/mm^3 or evidence of bleeding with thrombocytopenia	• Interrupt lenalidomide • Resume with dose reduced by 1 level once platelet count recovers to ≥ 30,000/mm^3 • For any recurrence, interrupt lenalidomide; resume with dose reduced by 1 level once platelets recover to ≥ 30,000/mm^3

Table 10b: Lenalidomide Dose Modifications for Hematologic Toxicities (post auto-HSCT)

Toxicity	Recommended Action
ANC < 500/mm^3	• Interrupt lenalidomide, follow CBC weekly • Resume at next lower dose continuously for Days 1-28 of repeated 28-day cycle once ANC recovers to ≥ 500/mm^3 • For any recurrence, interrupt lenalidomide; do not dose below 5mg daily. Resume at 5 mg daily.
Platelets < 30,000/mm^3 or evidence of bleeding with thrombocytopenia	• Interrupt lenalidomide, follow CBC weekly • Resume at next lower dose continuously for Days 1-28 of repeated 28-day cycle once platelet count recovers to ≥ 30,000/mm^3 • For any recurrence, interrupt lenalidomide; do not dose below 5mg. Resume at 5 mg daily.

6.3.2.2 Lenalidomide Dosing in Renal Impairment

Because lenalidomide is primarily excreted unchanged by the kidney, adjustments to the dose of lenalidomide are recommended in subjects with renal impairment. The recommended doses for subjects with multiple myeloma and renal impairment are shown in the table below.

Table 11: Lenalidomide Dose Modifications for Renal Impairment

Dose modifications related to creatinine clearance only apply to Day 1 of each cycle.

Renal Function in MM	Dose	Frequency
CrCl >60 mL/min	10 mg	Once Daily
CrCl 30-60 mL/min	5 mg	Once Daily
CrCl <30 mL/min (not requiring dialysis)	2.5 mg	Once Daily
CrCl <30 mL/min (requiring dialysis)	2.5 mg	Once Daily. On dialysis days, administer the dose following dialysis

6.3.2.3 Lenalidomide: Other Non-specified Non-Hematologic Toxicities

Table 12: Lenalidomide Dose Modifications for Non-Hematologic Toxicities

Toxicity	Recommended Action
Other ≥ Grade 3 non-hematologic toxicity[a]	• Hold dose; resume with dose reduced by 1 level once resolved to ≤ Grade 2
[a]Other than nausea, vomiting or diarrhea that responds to supportive care within 7 days, or Grade 3 fatigue or asthenia that lasts <7 days	

6.4 Dexamethasone

6.4.1 Administration

For induction, the dexamethasone total dose of 40 mg may be taken weekly, or at discretion of investigator, as a split dose of 20 mg over 2 consecutive days weekly during the 8 cycles of induction. On days when daratumumab is administered, the dexamethasone will serve as premedication given 1 to 3 hours prior to each daratumumab infusion (see Section 6.2.2). Note: If the dexamethasone split dose of 20 mg is given with daratumumab, the first 20 mg dose will be given on the first day of daratumumab.

For KRd consolidation, dexamethasone 20mg (or LTD from end of induction) is to be taken every 2 weeks (D1 and D15).

Refer to the following table for dexamethasone dose levels when dose reductions are required during induction:

Table 13: Dose Levels for Dexamethasone during Induction

Dose Level	Dose	Schedule
0*	40mg[1]	D1, 8, 15, 22
- 1	20mg	D1, 8, 15, 22
- 2	12mg	D1, 8, 15, 22

* Dose level 0 refers to the starting dose of dexamethasone during Induction
[1] At discretion of the investigator, dexamethasone may be administered as a split dose of 20 mg over 2 consecutive days weekly during the 8 cycles of induction.

Refer to the following table for dexamethasone dose levels when dose reductions are required during consolidation:

Table 14: Dose Levels for Dexamethasone during Consolidation

Dose Level	Dose	Schedule
0*	20mg	D1, 15
- 1	12mg	D1, 15
- 2	8mg	D1, 15

* Dose level 0 refers to the starting dose of dexamethasone during Consolidation

If dose reductions of dexamethasone beyond those levels listed in Tables 13 and 14, this agent should be permanently discontinued.

6.4.2 Dose Modifications for Dexamethasone-Related Toxicities

If a dose of dexamethasone is missed, the subject should not take an additional dose, but should take the next usual prescribed dose.

Table 15: Dexamethasone Dose Modifications for Non-Hematologic Toxicities

Toxicity	Recommendation Action
Dyspepsia, gastric or duodenal ulcer, gastritis **Grade 1-2** (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.

>Grade 3 (requiring hospitalization or surgery	Hold dexamethasone until symptoms adequately controlled. Restart dexamethasone reduced by 1 dose level; consider concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently.
Acute pancreatitis	Discontinue dexamethasone permanently.
Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone reduced by 1 dose level; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Confusion or mood alteration > Grade 2 (interfering with function +/– interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart dexamethasone reduced by 1 dose level. If symptoms persist despite above measures, reduce by another dose level.
Muscle weakness > Grade 2 (symptomatic and interfering with function +/– interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Hyperglycemia ≥ Grade 3	Treatment with insulin or other hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.
Other non-hematologic toxicity ≥ Grade 3 felt related to dexamethasone[a]	Hold dexamethasone dose. Resume dexamethasone reduced by 1 dose level when toxicity has resolved to ≤Grade 2 or to baseline. If toxicity recurs, discontinue dexamethasone permanently.
[a]Other than nausea, vomiting or diarrhea that responds to supportive care within 7 days, or Grade 3 fatigue or asthenia that was present at baseline or that lasts <7 days	

6.5 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Subjects may receive palliative radiation at the discretion of the Sponsor-Investigator.

6.6 Concomitant Medication

6.6.1 Recommended Medications

6.6.1.1 Bisphosphonates

For subjects who have not previously received bisphosphonates, bisphosphonates are

recommended for all subjects. Bisphosphonate therapy is recommended to be continued per treatment guidelines. In addition, denosumab use is also permitted.

6.6.1.2 Allopurinol

It is recommended that subjects at high risk for TLS (i.e., those with a high tumor burden, high LDH and/or high uric acid level before the start of treatment) be treated prophylactically in accordance with local standards including allopurinol 300 mg daily.

6.6.1.3 Anti-Viral

Acyclovir or equivalent antiviral should be given to all subjects to decrease the risk of herpes zoster reactivation, per institutional prophylaxis guidelines, unless contraindicated. In those subjects with a history of herpes zoster infection, antiviral prophylaxis should begin within 1 week after the initiation of daratumumab and continue until 3 months after daratumumab is discontinued.

Primary antiviral prophylaxis is permitted as per local standard of care for management of hepatitis B virus reactivation. HBV DNA testing is mandatory for subjects at risk for HBV reactivation. Refer to Section 7 for further details. For subjects 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 prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

6.6.1.4 Thromboprophylaxis

Thromboprophylaxis is recommended for all subjects receiving the combination of carfilzomib, lenalidomide and dexamethasone. The regimen of thromboprophylaxis should be based on an assessment of the subjects' underlying risks. Instruct subjects to report immediately any signs and symptoms suggestive of thrombotic events.

6.6.2 Prohibited Medications

Concomitant administration of investigational agents, other than those mandated by the protocol, are prohibited.

No investigational or commercial agents or therapies other than those described may be administered with the intent to treat the subject's malignancy.

6.6.3 Permitted Medications

Subjects may receive antiemetics and antidiarrheal agents as necessary. Myeloid growth factors may be used if neutropenia occurs but should not be given prophylactically. Subjects may receive platelet transfusions if clinically indicated in accordance with institutional guidelines Subjects should have anemia treated in accordance with the institutional guidelines (however, see Section 6.6.3.1).

All other treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

6.6.3.1 Precautionary Medications

If an erythropoietic stimulating agents (ESAs) is given for anemia, keep in mind that there is an increased risk of thrombosis with lenalidomide and carfilzomib. Include all concomitant medications that are not specifically prohibited but require additional monitoring during study treatment.

7. STUDY CALENDARS

Use the Induction Calendar for all enrolled subjects. Based on disease evaluation after induction, subjects will be divided into 3 separate treatment groups (see Schema 2). There is a separate Post-Induction Calendar for each group (Group A, Group B and Group C). After the post-induction disease evaluation, use the appropriate Post-Induction Calendar for a given subject.

7.1 INDUCTION CALENDAR (28-day cycles)

Study Procedures	**Screening[1]**	**Induction Cycles 1-2[2]**				**Induction Cycles 3-6[2]**				**Induction Cycles 7-8[2, 23]**				**Post-Induction Disease Evaluation[4]** (only for subjects who complete induction)	**Safety Follow-up[24]** (only subjects who permanently discontinue induction early and do not have a Post-Induction visit)	**Follow-up[25]** (only subjects who permanently discontinue induction early and do not have a Post-Induction visit)	**Go to appropriate post-induction calendar (A, B or C) based on the MRD based treatment algorithm (see Schema 2)**
Study Day		**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22[3]**	**1**	**8**	**15**	**22[3]**				
Informed Consent	X																
Medical history	X																
Physical exam[5]	X	Symptom-directed physical exam only															
Weight[6]	X	X				X				X							
ECOG Performance status	X	X				X				X				X	X		
Vital signs[7]	X	X	X	X	X	X		X		X							
ECG	X[26]	X[1]				X				X				X	X		
ECHO or MUGA	X[26]																
Forced expiratory volume test (subjects with COPD)	X																
Hepatitis B (HBV) virus serology[20]	X																
HBV DNA testing[21]	X	Every 12 weeks up to 6 months after last dose of Dara															
Blood type and screen[8]		X															
Serum chemistries[9]	X[9]	X[1]	X	X		X		X		X		X		X	X		
CBCD[10, 30]	X	X[1]	X	X	X	X		X		X		X		X	X		
Pregnancy test[11]	X[11]	X	X	X	X	X				X							
AEs & concomitant meds	X	Monitor continuously (see Section 12.3 for timing of AE/SAE collection)															
Serum beta2-microglobulin[19]	X																
Blood and urine for disease evaluation[12, 19]	X	X				X				X				X		X	
Daratumumab Interference Testing		At suspected CR; subjects with IgG Kappa MM only															
Bone marrow aspirate and biopsy for disease assessment and MRD[13]	X													X	X[27]		
Skeletal Survey[14]	X	As clinically indicated															

Assess extramedullary plasmacytomas[15]	X													X		
Carfilzomib[16]		X	X	X		X	X	X		X	X	X				
Lenalidomide[29]		Days 1-21 (oral)				Days 1-21 (oral)				Days 1-21 (oral)						
Dexamethasone[17]		X	X	X	X	X	X	X	X	X	X	X	X			
Daratumumab[22]		X	X	X	X	X		X		X						
Blood sample for correlatives[18]		Collect D1 of cycles 1, 3, 5 and 7												X		
Stem cell mobilization/collection[28]		May be done any time after Cycle 3 of induction per investigator discretion														
Documentation of survival and occurrence of secondary malignancies		X														
Disease Evaluation Confirmation Data Capture[31]		X														

Key to Footnotes for Induction

[1] Within 28 days prior to induction cycle 1 day 1 (C1D1) unless otherwise noted; if screening hematology and serum chemistries were performed within 7 days of induction C1D1, these do not need to be repeated C1D1; if screening ECG was performed within 14 days of induction C1D1, an ECG does not need to be repeated C1D1.

[2] A window of +/- 2 days will be applied to all induction treatment study visits except for blood and urine disease evaluation on Day1 of each cycle. Day 1 blood and urine disease evaluation must be done within 7 days prior to Cycle 1 Day 1 (starting with cycle 2, urine disease evaluation can be ±7 days of Day 1 of each cycle, blood disease evaluation must remain within 7 days prior to Day 1). This includes study treatment and required protocol procedures prior to dosing. Every effort should be made to maintain consecutive dosing days.

[3] There is no study visit required on D22 of induction cycles 3-8; however, weekly oral dexamethasone schedule includes D22

[4] The primary endpoint (CR or better post induction) will be assessed at the post-induction disease evaluation.

[5] Complete physical exam, including height and neurologic exam to detect peripheral neuropathy, at screening. Thereafter symptom-directed physical exam only. During the COVID-19 pandemic, virtual visits may be performed starting with Cycle 2 of induction per investigator discretion.

[6] If a subject's weight changes by more than 20% from induction C1D1, the dose of carfilzomib should be re-calculated.

[7] Vital signs to include temperature, pulse rate, blood pressure and respiratory rate. Measure at the following time points: For all daratumumab injections, vital signs will be measured per institutional standards but at a minimum prior to the start of injection for all doses. Vital signs at the end of the injection only required for C1D1 and C1D8 and thereafter per investigator discretion. Subject should remain in clinic for at least 1 hour observation period for the first dose of daratumumab and the first of carfilzomib on study, and per investigator discretion for subsequent doses.

[8] ABO and Rh blood typing and indirect antiglobulin test (also known as indirect Coombs test) to be performed any time between screening and initiation of study treatment. It is recommended that the subject carry a card with the blood antigen profile at all times during the study.

[9] Serum chemistries: BUN, creatinine (with calculated creatinine clearance at Screening and on Day 1 of each cycle), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.

[10] CBCD: complete blood count with differential and platelets

[11] Serum or urine B-HCG in FCBP within 24 hours prior to induction C1D1. Pregnancy testing (serum or urine) must be repeated once a week (D1, 8, 15, 22) in induction cycle 1, and then monthly (D1 of each cycle) for subsequent cycles in FCBP.

[12] Tests to include: serum quantitative immunoglobulins (QIg; including IgA, IgM, IgG, IgD**, IgE**), serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP; 24-hr urine sample required), serum and urine immunofixation, and serum free light chain (FLC). If screening tests were performed within 14 days of induction C1D1, these do not need to be repeated C1D1. Day 1 blood and urine disease evaluation must be done within 7 days prior to Cycle 1 Day 1 (starting with cycle 2, urine disease evaluation can be ±7 days of Day 1 of each cycle, blood disease evaluation must remain within 7 days prior to Day 1).
**Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed on D1 of each cycle for subjects with light chain only disease only. After screening assessments, subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated. At the post-induction disease evaluation, serum FLC to be performed in subjects with light chain only disease and in subjects where at least a CR is suspected or are maintaining at least a CR.

[13] Bone marrow aspirate and biopsy collected for disease assessment and MRD* analyses/correlatives (see Section 8.6.2). If a fresh biopsy is not collected at screening, may use non-decalcified diagnostic tissue (i.e., bone marrow aspirate slides or FFPE tissue) if collected within 6 months of enrollment. Please see laboratory guidelines for details. *At post-induction disease evaluation, only those subjects who experience ≥VGPR will undergo an assessment of MRD. All other subjects will be considered MRD (+). **NOTE:** MRD will be evaluated via flow cytometry and DNA sequencing. The MRD result evaluated via DNA sequencing will be used to determine treatment decisions. If a subject has disease progression/relapse and a bone marrow aspirate is performed as part of clinical care, bone marrow samples will be collected for correlatives as described in Section 8.6.2 and the laboratory guidelines. Bone marrow samples taken for disease evaluation purposes where MRD is not required to be assessed should still be collected for banking and should include up to 12 ml whenever possible.

[14] Acceptable for screening if performed as part of standard of care within 42 days prior to day 1 of study treatment. For subjects who received prior therapy, skeletal survey must have been performed no earlier than 42 days prior to initiation of the pre-study induction cycle. If a skeletal survey was not performed prior to initiation of the pre-study induction cycle, it is acceptable if skeletal survey is performed after initiation of the pre-study induction cycle as long as it is performed prior to initiation of study treatment.

[15] Assess extramedullary plasmacytomas using PET/CT and/or Whole Body (WB)-MRI. Acceptable for screening if performed as part of standard of care within 42 days prior to initiation of the pre-study induction cycle (subjects who received prior therapy) or within 42 days of day 1 of study treatment (subjects with no prior therapy). For subjects who received prior therapy, the skeletal survey or CT will be acceptable and PET/CT/Whole Body MRI is not required.

[16] See Section 6.1 for required hydration and additional information regarding cycle 1 dosing

[17] See Section 6.4 for dosing instructions. On days when daratumumab is administered, protocol-directed dexamethasone will serve as premedication given 1 to 3 hours prior to each daratumumab infusion (see Section 6.2).

[18]Approximately 30 mL of blood will be collected pre-treatment D1 of cycles 1, 3, 5 and 7, and at the post-induction disease evaluation. See Section 8.6.1 for detailed information on blood sample acquisition.

[19] Unless otherwise noted, all baseline disease assessments must be completed within 28 days of initiation of the first pre-study induction cycle (subjects who received prior therapy) or within 28 days of day 1 of study treatment (subjects with no prior therapy). **Subjects who received a cycle of prior therapy:** If a UPEP and/or urine IFE was not collected prior to initiation of pre-study induction, this will not be considered a deviation as long as the subject has evidence of measurable disease by another assessment (SPEP, FLC, etc). If a serum beta-2 microglobulin was not collected prior to initiation of pre-study induction, this will not be considered a deviation. Collection of serum beta-2 microglobulin at screening is not required if previously collected prior to initiating pre-study induction.

[20] Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc).

[21] For subjects with serologic evidence of resolved HBV infection (i.e. positive anti-HBs or positive anti-HBc) at Screening. HBV DNA testing must be performed locally. 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. During and following study treatment, subjects who have a history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the study calendar. Results of HBV testing may be reported to the local health authorities.
[22] Per Investigator's discretion, for subjects at higher risk for pulmonary complications that are not hospitalized for monitoring after daratumumab infusion , a follow-up telephone call should be made and documented to monitor their condition within 48 hours (no later than 72 hours) after all daratumumab infusions.
[23] For subjects who completed a pre-study cycle of induction chemotherapy, only 7 cycles of KRdD Induction should be given.
[24] This visit should occur in subjects 30 days (+/-10 days) after study treatment stops for whatever reason.
[25] Only for subjects who permanently discontinue induction prior to completion of 8 cycles. **PFS (progression-free survival) Follow-up:** Subjects who have not progressed and permanently discontinued treatment for reasons per Section 9.2 will go into PFS Follow Up. Subjects in PFS Follow-up should continue to have disease evaluations per standard of care until confirmed disease progression, start of new anti-cancer treatment, or meet the off study criteria in Section 9.2, whichever occurs first. **Survival Follow-up:** Subjects who have permanently discontinued study treatment and have confirmed progression or initiated new anti-cancer treatment will go into Survival Follow-up every 6 months (+/- 30 days) from the date of disease progression or initiation of subsequent anti-cancer treatment until off study criteria in Section 9.2 are met. Survival Follow-up may be conducted via telephone. Any second primary malignancies discovered during the subject's participation in the study will be documented.
[26] **Subjects who received a cycle of pre-study induction:** Echo or MUGA and/or ECG does not need to be repeated during screening if previously performed prior to initiation or during cycle of pre-study induction.
[27] If a subject has disease progression/relapse and a bone marrow aspirate is performed as part of clinical care, bone marrow samples will be collected for disease evaluation and correlatives as described in Section 8.6.2 and the laboratory guidelines.
[28] Per Investigator discretion for transplant eligible subjects, induction treatment may be delayed for stem cell mobilization/collection and held until subjects have recovered. This will not be considered a deviation. Given difficulties with stem cell mobilization later during KRD-dara induction, initial attempt at stem cell collection is preferred after C3 or C4 of induction (see Section 5.2).
[29] If dosing with lenalidomide is delayed due to an extenuating circumstance (e.g., needing a new prescription due to dose reduction), a delay of up to 5 days will not be considered a deviation.
[30] CBCD only required in C1 and C2 on days subject is coming on-site to receive study treatment (i.e., receiving C3 dosing in C2 due to receiving a pre-study cycle of induction).
[31] For disease evaluation, please refer to footnotes * and II in the IMWG criteria, see Section 13. All response categories require two consecutive assessments, which should be captured in the dataset. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The confirmatory scan data should be entered into the database.

7.2 POST-INDUCTION CALENDAR: GROUP A (28-day cycles)

Study Procedures	**Stem Cell Mobilization and Collection[1]**	**Lenalidomide Maintenance Cycles 1-12**	**Lenalidomide Maintenance Cycles 13+**	**Safety Follow-up Visit[3]**	**PFS Follow Up[4]**	**Survival Follow-up[15]**
Study Day		**D1[2]**	**D1 every three cycles[2]**		**per standard of care**	**Q 6 months +/- 30 days**
Physical exam[14]		Symptom-directed physical exam only				
ECOG Performance status		X		X		
Serum chemistries[5]		X		X		
CBCD[6]		X		X		
Pregnancy test[7]		X[7]		X[7]		
AEs & concomitant medications		Monitor continuously until 30 days after the last dose of study treatment				
Blood and urine for disease evaluation[8]		X		X	X	
Daratumumab Interference Testing		At suspected CR; subjects with IgG Kappa MM only				
Bone marrow aspirate and biopsy for disease assessment and MRD[9]		See footnote #9				
Skeletal Survey		As clinically indicated				
Assess extramedullary plasmacytomas[10]		See footnote #10				
Lenalidomide[12]		Days 1-21 (oral) each cycle				

Blood sample for correlatives[11]		See footnote #11		
Documentation of survival and occurrence of secondary malignancies		X		
Disease Evaluation Confirmation Data Capture[16]		X		
HBV DNA testing[13]		Every 12 weeks up to 6 months after last dose of Dara		

Key to Footnotes for Post-Induction Group A

[1] Subjects who are considered eligible for transplant at the discretion of the investigator will undergo stem cell mobilization with the hematopoietic growth factor G-CSF (filgrastim or equivalent) with or without the CXCR4 antagonist plerixafor, as per institutional standards. For subjects who fail collection of adequate stem cells during induction or post-induction, re-attempts at mobilization and stem cell collection are acceptable during maintenance therapy per investigator discretion. Collection and freezing of stem cells should be performed as per institutional standards. AEs related to mobilization do not need to be reported. However, any AEs considered related to induction (i.e., either daratumumab, carfilzomib, lenalidomide and/or dexamethasone) should continue to be reported. If prescribed, lenalidomide maintenance may begin after recovery from stem cell mobilization and collection. Treatment can be held during mobilization/ collection per investigator discretion and it will not be considered a protocol deviation.

[2] Lenalidomide maintenance is at the discretion of the investigator. For subjects on lenalidomide maintenance, study visits will occur once every 28 days for the first year (D1 of each cycle for cycles 1-12), and then every 12 weeks (3 cycles, i.e., D1 cycle 13, cycle 16, etc.) for subsequent years. A window of +/-7 days will be applied to all lenalidomide maintenance visits during the first year (cycles 1-12). A window of +/-15 days will be applied to all subsequent lenalidomide maintenance visits (cycles 13+). Windows include study treatment and required protocol procedures prior to dosing, except bone marrow biopsy which is not required prior to treatment.

[3] This visit should occur in subjects 30 days (+/-10 days) after study treatment stops for whatever reason (toxicity, progression, or at discretion of the investigator). For subjects who do not go on lenalidomide maintenance, this visit may occur the day of (but prior to) stem cell mobilization (if the subject is eligible for transplant) if stem cell mobilization is scheduled.

NOTE: subjects who have ongoing Grade 4 AE or SAE at the time of the Safety Follow-up Visit will continue to be followed until the event is resolved or deemed irreversible by the investigator.

[4] PFS (progression-free survival) Follow-up: Subjects who do not receive lenalidomide maintenance or subjects who initiate lenalidomide maintenance but permanently discontinue study treatment for reasons in Section 9.2 except disease progression will go into PFS Follow Up. Subjects in PFS Follow-up should continue to have disease evaluations per standard of care until confirmed disease progression, start of new anti-cancer treatment, or meet the off study criteria in Section 9.2, whichever occurs first. . Any second primary malignancies discovered during the subject's participation in the study will be documented. If confirmed PD occurs or new anti-cancer treatment is initiated, subjects will enter Survival Follow-up.

[5] Serum chemistries: BUN, creatinine (with calculated creatinine clearance on Day 1 of each cycle), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.

[6] CBCD: complete blood count with differential and platelets

[7] Pregnancy testing (serum or urine) must be repeated monthly while on lenalidomide treatment (D1 of each cycle) in FCBP. Not required for subjects who are not receiving lenalidomide treatment. Pregnancy testing may be done at a local medical office at the discretion of the investigator.

[8] Tests to include: serum quantitative immunoglobulins (QIg; including IgA, IgM, IgG, IgD[**], IgE[**]), serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP; 24-hr urine sample required), serum and urine immunofixation, and serum free light chain (FLC). [**]Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated. Serum FLC to be performed for subjects with light chain only disease and for subjects with a suspected CR or are maintaining at least a CR. Day 1 blood disease evaluation must be done within 7 days prior to Day 1. Urine disease evaluation may be done ±7 days of Day 1.

[9] For subjects on lenalidomide maintenance and PFS follow-up, bone marrow aspirate and biopsy should be performed for disease evaluation and MRD/correlatives at 6 and 12 months (each +/- 15 days) after the Post-Induction disease evaluation. After the 12-month Post-Induction evaluation, bone marrow aspirate and biopsy should be performed annually (+/- 30 days)(see Section 8.6.2 and the laboratory guidelines for detailed information) until disease progression or initiation of new anti-cancer treatment. **NOTE:** MRD will be evaluated via flow cytometry and DNA sequencing only in subjects who experience ≥ VGPR. All other subjects will be considered MRD (+). If a subject has disease progression/relapse and a bone marrow aspirate is performed as part of clinical care, bone marrow samples will be collected for correlatives as described in Section 8.6.2 and the laboratory guidelines. Bone marrow samples taken for disease evaluation purposes where MRD is not required to be assessed should still be collected for banking and should include up to 12 mL whenever possible.

[10] For subjects with extramedullary plasmacytomas present at post-induction, PET/CT and/or WB-MRI every 12 weeks for the first year, and then once a year for subsequent years (or as clinically indicated).

[11] Approximately 30 mL of blood will be collected D1 of cycles 3, 5, 7, 9 and 11. An additional blood sample will be collected at progression. See Section 8.6.1 and the laboratory guidelines for detailed information.

[12] Not required for subjects not receiving lenalidomide treatment. For subjects receiving lenalidomide for maintenance, creatinine clearance should be reviewed, and dosing followed per Section 6.3.2.2. If dosing with lenalidomide is delayed due to an extenuating circumstance (e.g., needing a new prescription due to dose reduction), a delay of up to 5 days will not be considered a deviation.

[13] For subjects with serologic evidence of resolved HBV infection (i.e. positive anti-HBs or positive anti-HBc) at Screening. HBV DNA testing must be performed locally. 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. During and following study treatment, subjects who have a history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the study calendar. Results of HBV testing may be reported to the local health authorities.

[14] During the COVID-19 pandemic, virtual visits may be performed per investigator discretion.

[15] Subjects who have permanently discontinued study treatment and have confirmed progression or initiated new anti-cancer treatment will go into Survival Follow-up every 6 months (+/- 30 days) from the date of disease progression or initiation of subsequent anti-cancer treatment until off study criteria in Section 9.2 are met. Survival Follow-up may be conducted via telephone. Any second primary malignancies discovered during the subject's participation in the study will be documented.

[16] For disease evaluation, please refer to footnotes * and II in the IMWG criteria, see Section 13. All response categories require two consecutive assessments, which should be captured in the database. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The confirmatory scan data should be entered into the database.

7.3 POST-INDUCTION CALENDAR: GROUP B (28-day cycles)

Study Procedures	ASCT [1]	Post-ASCT Disease Evaluation[2]	KRd Consolidation Cycles 1-12[3]			Post-Consolidation Disease Evaluation[5]	Lenalidomide Maintenance Cycles 1-12	Lenalidomide Maintenance Cycles 13+	Safety Follow-up Visit[7]	PFS Follow-up[8]	Survival Follow-up[21]
Study Day			**D1[4]**	**D8**	**D15[4]**		**D1[6]**	**D1 every three cycles[6]**		**Per standard of care**	**Q 6 months +/- 30 days**
Physical exam[20]		Symptom-directed physical exam only									
Weight[9]			X[9]								
ECOG Performance status		X	X			X	X	X	X		
ECG[10]			X			X					
Serum chemistries[11]		X	X		X	X	X	X	X		
CBCD[12]		X	X		X	X	X	X	X		
Pregnancy test[13]			X				X[18]	X[18]			
AEs & concomitant medications		Monitor continuously until 30 days after the last dose of study treatment									
Blood and urine for disease evaluation[14]		X	X			X	X	X		X	
Daratumumab Interference Testing		At suspected CR; subjects with IgG Kappa MM only									
Bone marrow aspirate and biopsy for disease assessment and MRD[15]		X	X[3]			X	See footnote #15				
Skeletal Survey		As clinically indicated									
Assess extramedullary plasmacytomas[16]		See footnote #16									
Carfilzomib			X	X	X						
Lenalidomide[18]			Days 1-21 (oral)[18]				Days 1-21 (oral) each cycle[18]				
Dexamethasone			X		X						

Blood sample for correlatives[17]		See footnote #17		
HBV DNA testing[19]		Every 12 weeks up to 6 months after last dose of Dara		
Documentation of survival and occurrence of secondary malignancies		X		
Disease Evaluation Confirmation Data Capture[22]		X		

Key to Footnotes for Post-Induction Group B

[1] Subjects will undergo stem cell mobilization with the hematopoietic growth factor G-CSF (filgrastim or equivalent) with or without the CXCR4 antagonist plerixafor, as per institutional standards, if not done during induction per investigator discretion. Collection and freezing of stem cells should be performed as per institutional standards. After recovery from stem cell mobilization and collection, high dose melphalan should be administered followed by ASCT, as per institutional standards, including any necessary prophylactic antibiotics, hematopoietic growth factors, and other supportive care during and post ASCT. AEs related to mobilization, HDC and ASCT do not need to be reported. However, any AEs considered related to induction (i.e., either daratumumab, carfilzomib, lenalidomide and/or dexamethasone) should continue to be reported.

[2] Disease evaluation after ASCT will take place after engraftment is complete, as defined per institutional standards. Any subject who converts to MRD (-) disease via DNA sequencing after ASCT may receive lenalidomide maintenance until relapse or progression or no further treatment (skip to lenalidomide maintenance section of the calendar), at the discretion of the investigator. Any subject who is MRD (+) via DNA sequencing after ASCT will receive up to 12 cycles of KRd consolidation (see footnote #3). Lenalidomide maintenance or KRd consolidation can be initiated at the discretion of the investigator after disease evaluation and recovery from ASCT (~60-100 days post ASCT).

[3] The number of cycles of KRd will depend on the MRD status (based on MRD result evaluated via DNA sequencing) during treatment. A bone marrow aspirate and biopsy will be performed after completion of cycle 4 and cycle 8 of KRd (if applicable) for disease evaluation and to assess MRD/correlatives only in subjects with ≥VGPR based on blood and urine evaluation [all other subjects will be considered MRD (+)]. The MRD result evaluated via DNA sequencing will be used to determine treatment decisions. There may be a delay in initiating C5D1 and C9D1 (if applicable) of KRd consolidation until disease assessment and MRD via DNA sequencing (if applicable) results are available. Those who convert to MRD (-) via DNA sequencing after cycle 4 or cycle 8 will permanently discontinue KRd and may receive lenalidomide maintenance until relapse or progression or no further treatment, at the discretion of the investigator (skip to lenalidomide maintenance section of the calendar). For those subjects, this disease evaluation may serve as their post-consolidation disease evaluation. **NOTE:** MRD will be evaluated via flow cytometry and DNA sequencing (see Section 8.6.2).

[4] A window of +/-2 days will be applied to all KRd consolidation study visits except for blood and urine disease evaluation on Day1 of each cycle. Day 1 blood disease evaluation must be done within 7 days prior to Day 1. Urine disease evaluation may be done ±7 days of Day 1. This includes study treatment and required protocol procedures prior to dosing.

[5] Any subject who converts to MRD (-) disease via DNA sequencing during or after KRd consolidation may receive lenalidomide maintenance until relapse or progression or no further treatment, at the discretion of the investigator. For those subjects who convert to MRD (-) disease and permanently discontinue KRd prior

to completing 12 cycles, the C1D1 Lenalidomide Maintenance visit may serve as the Post-Consolidation disease evaluation visit at the investigator's discretion. The EKG required at the Post-Consolidation visit should be done at the C1D1 Lenalidomide Maintenance timepoint. Those who have MRD (+) disease via DNA sequencing after 12 cycles of KRd consolidation **will** receive lenalidomide maintenance until relapse or progression.

Note: If MRD results have been positive at previous timepoints, and physician plans to continue lenalidomide regardless of Post-Consolidation MRD results, then the C1D1 Maintenance visit may serve as the Post-Consolidation disease evaluation visit. For these same subjects, they may also begin lenalidomide on C1D1 Maintenance visit per investigator discretion.

[6] For subjects on lenalidomide maintenance, study visits will occur once every 28 days for the first year (D1 of each cycle for cycles 1-12), and then every 12 weeks (3 cycles, i.e., D1 cycle 13, cycle 16, etc.) for subsequent years. A window of +/-7 days will be applied to all lenalidomide maintenance visits during the first year (cycles 1-12). A window of +/- 15 days will be applied to all subsequent lenalidomide maintenance visits (cycles 13+). This window includes study treatment and required procedures prior to dosing, except bone marrow biopsy which is not required prior to treatment.

[7] This visit should occur in subjects 30 days (+/-10 days) after treatment stops for whatever reason (toxicity, progression, or at discretion of the investigator). For subjects who do not go on lenalidomide maintenance after ASCT, this visit may occur the day of Post-ASCT Disease Evaluation. **NOTE:** subjects who have ongoing Grade 4 AE or SAE at the time of the Safety Follow-up Visit will continue to be followed until the event is resolved or deemed irreversible by the investigator.

[8] PFS (progression-free survival) Follow-up: Subjects who permanently discontinue study treatment for reasons other than disease progression as per Section 9.2, will go into PFS Follow Up. Subjects in PFS Follow-up should continue to have disease evaluations per standard of care until confirmed disease progression, start of new anti-cancer treatment, or meet the off study criteria in Section 9.2, whichever occurs first. Any second primary malignancies discovered during the subject's participation in the study will be documented. If confirmed PD occurs or new anti-cancer treatment is initiated, subjects will enter Survival Follow-up.

[9] If a subject's weight changes by more than 20% from KRd consolidation C1D1, the dose of carfilzomib should be recalculated.

[10] An ECG should be performed D1 of KRd consolidation cycles 1, 4 and, if applicable, cycles 7 and 11, and then at the post-consolidation disease evaluation.

[11] Serum chemistries: BUN, creatinine (with calculated creatinine clearance on Day 1 of each cycle), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.

[12] CBCD: complete blood count with differential and platelets

[13] Pregnancy testing (serum or urine) must be repeated monthly while on lenalidomide treatment (D1 of each cycle of KRd or lenalidomide) in FCBP. Not required for subjects not receiving lenalidomide treatment. Pregnancy testing may be done at a local medical office at the discretion of the investigator.

[14] Tests to include: serum quantitative immunoglobulins (QIg; including IgA, IgM, IgG, IgD**, IgE**), serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP; 24-hr urine sample required), serum and urine immunofixation, and serum free light chain (FLC). **Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated. Serum FLC to be performed for subjects with light chain only disease and for subjects with a suspected CR or who are maintaining at least a CR. Day 1 blood disease evaluation must be done within 7 days prior to Day 1. Urine disease evaluation may be done ±7 days of Day 1.

[15] Bone marrow aspirate and biopsy collected at the following time-points for disease evaluation and MRD analyses/correlatives (see Section 8.6.2 and laboratory guidelines for detailed information): Post-ASCT visit, during KRd consolidation as referenced above in Footnote #3, and the Post-Consolidation visit. During maintenance and PFS follow up: Bone marrow aspirate and biopsy should be performed for disease evaluation and MRD/correlatives at 6, and 12 months (each +/- 15 days) after the Post-Consolidation disease evaluation, and then annually (+/- 30 days) until disease progression or initiation of new anti-cancer treatment. For subjects who convert to MRD (-) after ASCT and do not receive consolidation, bone marrow aspirate and biopsy for disease evaluation and MRD analysis/correlatives should be evaluated at 6 and 12 months (each +/- 15 days) after transplant. **NOTE:** MRD will be evaluated via flow cytometry and DNA sequencing only in subjects who experience ≥ VGPR. All other subjects will be considered MRD (+). If a subject has disease progression/relapse and a bone marrow aspirate is performed as part of clinical care, bone marrow samples will be collected for correlatives as described in Section 8.6.2 and the laboratory

guidelines. Bone marrow samples taken for disease evaluation purposes where MRD is not required to be assessed should still be collected for banking and should include up to 12mL whenever possible.
[16] For subjects with extramedullary plasmacytomas present at the post-induction assessment, PET/CT and/or WB-MRI every 12 weeks during KRd consolidation and for the first year of lenalidomide maintenance, and then once a year for subsequent years (or as clinically indicated).
[17] Approximately 30 mL of blood will be collected at the post-ASCT disease evaluation, pre-treatment every 4 cycles during KRd consolidation (C5D1 and C9D1), and D1 of lenalidomide maintenance (if applicable) cycles 1, 3, 5, 7, 9 and 11. An additional blood sample will be collected at progression. See Section 8.6.1 and the laboratory guidelines for detailed information.
[18] Not required for subjects not receiving lenalidomide treatment. For subjects receiving lenalidomide for maintenance, creatinine clearance should be reviewed, and dosing followed per Section 6.3.2.2. If dosing with lenalidomide is delayed due to an extenuating circumstance (e.g., needing a new prescription due to dose reduction), a delay of up to 5 days will not be considered a deviation.
[19] For subjects with serologic evidence of resolved HBV infection (i.e. positive anti-HBs or positive anti-HBc) at Screening. HBV DNA testing must be performed locally. 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. During and following study treatment, subjects who have a history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the study calendar. Results of HBV testing may be reported to the local health authorities.
[20] During the COVID-19 pandemic, virtual visits may be performed per investigator discretion.
[21] Subjects who have permanently discontinued study treatment and have confirmed progression or initiated new anti-cancer treatment will go into Survival Follow-up every 6 months (+/- 30 days) from the date of disease progression or initiation of subsequent anti-cancer treatment until off study criteria in Section 9.2 are met. Survival Follow-up may be conducted via telephone. Any second primary malignancies discovered during the subject's participation in the study will be documented.
[22] For disease evaluation, please refer to footnotes * and II in the IMWG criteria, see Section 13. All response categories require two consecutive assessments, which should be captured in the dataset. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The confirmatory scan data should be entered into the dataset.

7.4 POST-INDUCTION CALENDAR: GROUP C (28-day cycles)

Study Procedures	**KRd Consolidation Cycles 1-12[1]**			**Post-Consolidation Disease Evaluation[3]**	**Lenalidomide Maintenance Cycles 1-12**	**Lenalidomide Maintenance Cycles 13+**	**Safety Follow-up Visit[5]**	**PFS Follow Up[6]**	**Follow-up[19]**
Study Day	**D1[2]**	**D8**	**D15[2]**		**D1[4]**	**D1 every three cycles[4]**		**Per standard of care**	**Q 6 months +/- 30 days**
Physical exam[18]	Symptom-directed physical exam only								
Weight[7]	X								
ECOG Performance status	X			X	X	X	X		
ECG[8]	X			X					
Serum chemistries[9]	X		X	X	X	X	X		
CBCD[10]	X		X	X	X	X	X		
Pregnancy test[11]	X				X[16]	X[16]			
AEs & concomitant medications	Monitor continuously until 30 days after the last dose of study treatment								
Blood and urine for disease evaluation[12]	X			X	X	X		X	
Daratumumab Interference Testing	At suspected CR; subjects with IgG Kappa MM only								
Bone marrow aspirate and biopsy for disease assessment and MRD[13]	X[1]			X	See footnote #13				
Skeletal Survey	As clinically indicated								
Assess extramedullary plasmacytomas[14]	See footnote #14								
Carfilzomib	X	X	X						
Lenalidomide[16]	Days 1-21 (oral)[16]				Days 1-21 (oral) each cycle[16]				
Dexamethasone	X		X						

Blood sample for correlatives[15]	See footnote #15			
HBV DNA testing[17]	Every 12 weeks up to 6 months after last dose of Dara			
Documentation of survival and occurrence of secondary malignancies	X			
Disease Evaluation Confirmation Data Capture[20]	X			

Key to Footnotes for Post-Induction Group C

[1] The number of cycles of KRd will depend on the MRD status (based on MRD results evaluated via DNA sequencing) during treatment. A bone marrow aspirate and biopsy will be performed after completion of cycle 4 and cycle 8 of KRd (if applicable) for disease evaluation and to assess MRD/correlatives in subjects with ≥VGPR based on blood and urine evaluation [all other subjects will be considered MRD ([+)]. The MRD result evaluated via DNA sequencing will be used to determine treatment decisions. There may be a delay in initiating C5D1 and C9D1 (if applicable) of KRd consolidation until disease assessment and MRD via DNA sequencing (if applicable) results are available. Those who convert to MRD (-) after cycle 4 or cycle 8 will permanently discontinue KRd and may receive lenalidomide maintenance until relapse or progression or no further treatment, at the discretion of the investigator (skip to lenalidomide maintenance section of the calendar). For those subjects, this disease evaluation may serve as their post-consolidation disease evaluation. **NOTE:** MRD will be evaluated via flow cytometry and DNA sequencing (see Section 8.6.2).

[2] A window of +/- 2 days will be applied to all KRd consolidation study visits except for blood and urine disease evaluation on Day1 of each cycle. Day 1 blood disease evaluation must be done within 7 days prior to Day 1. Urine disease evaluation may be done ±7 days of Day 1. This includes study treatment and required protocol procedures prior to dosing.

[3] Any subject who converts to MRD (-) disease after 12 cycles of KRd consolidation may receive lenalidomide maintenance until relapse or progression or no further treatment, at the discretion of the investigator. For those subjects who convert to MRD (-) disease and permanently discontinue KRd prior to completing 12 cycles, the C1D1 Lenalidomide Maintenance visit may serve as the Post-Consolidation disease evaluation visit at the investigator's discretion. The EKG required at the Post-Consolidation visit should be done at the C1D1 Lenalidomide Maintenance timepoint. Those who have MRD (+) disease via DNA sequencing after KRd consolidation **will** receive lenalidomide maintenance until relapse or progression.

Note: If MRD results have been positive at previous timepoints, and physician plans to continue lenalidomide regardless of Post-Consolidation MRD results, then the C1D1 Maintenance visit may serve as the Post-Consolidation disease evaluation visit. For these same subjects, they may also begin lenalidomide on C1D1 Maintenance visit per investigator discretion.

[4] For subjects on lenalidomide maintenance, study visits will occur once every 28 days for the first year (D1 of each cycle for cycles 1-12), and then every 12 weeks (3 cycles, i.e., D1 cycle 13, cycle 16, etc.) for subsequent years. A window of +/- 7 days will be applied to all lenalidomide maintenance visits during the first year (cycles 1-12). A window of +/- 15 days will be applied to all subsequent lenalidomide maintenance visits (cycles 13+). This window includes study treatment and required procedures prior to dosing, except bone marrow biopsy which is not required prior to treatment.

[5] This visit should occur in subjects 30 days (+/-10 days) after treatment stops for whatever reason (toxicity, progression, or at discretion of the investigator). For subjects who do not initiate lenalidomide maintenance after Post-Consolidation, this visit may occur the day of Post-Consolidation Disease evaluation. **NOTE:** subjects who have ongoing Grade 4 AE or SAE at the time of the Safety Follow-up Visit will continue to be followed until the event is resolved or deemed irreversible by the investigator.

[6] PFS (progression-free survival) Follow-up: Subjects who permanently discontinue study treatment for reasons other than disease progression as per Section 9.2 will go into PFS follow up. Subjects in PFS Follow-up should continue to have disease evaluations per standard of care until confirmed disease progression, start of new anti-cancer treatment, or meet the off study criteria in Section 9.2, whichever occurs first. Any second primary malignancies discovered during the subject's participation in the study will be documented. If confirmed PD occurs or new anti-cancer treatment is initiated, subjects will enter Survival Follow-up.

[7] If a subject's weight changes by more than 20% from KRd consolidation C1D1, the dose of carfilzomib should be recalculated.

[8] An ECG should be performed D1 of KRd consolidation cycles 1, 4, and, if applicable, cycles 7 and 11, and then at the post-consolidation disease evaluation.

[9] Serum chemistries: BUN, creatinine (with calculated creatinine clearance on Day 1 of each cycle), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.

[10] CBCD: complete blood count with differential and platelets

[11] Pregnancy testing (serum or urine) must be repeated monthly while on lenalidomide treatment (D1 of each cycle of KRd or lenalidomide) in FCBP. Not required for subjects on observation. Pregnancy testing may be done at a local medical office at the discretion of the investigator.

[12] Tests to include: serum quantitative immunoglobulins (QIg; including IgA, IgM, IgG, IgD**, IgE**), serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP; 24-hr urine sample required), serum and urine immunofixation, and serum free light chain (FLC). **Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated. Serum FLC to be performed for subjects with light chain only disease and for subjects with a suspected CR or who are maintaining at least a CR. Day 1 blood disease evaluation must be done within 7 days prior to Day 1. Urine disease evaluation may be done ±7 days of Day 1.

[13] Bone marrow aspirate and biopsy collected at the following time-points for disease assessment and MRD analyses/correlatives (see Section 8.6.2 and the laboratory guidelines for detailed information): During KRd consolidation as referenced above in Footnote #1, and the Post-consolidation visit. During maintenance/ PFS follow up: bone marrow aspirate and biopsy should be performed for disease evaluation and MRD at 6 and 12 months (each +/- 15 days) from the Post-Consolidation disease evaluation, and then annually (+/- 30 days) until disease progression or initiation of new anti-cancer treatment. **NOTE:** MRD will be evaluated via flow cytometry and DNA sequencing only in subjects who experience ≥ VGPR. All other subjects will be considered MRD (+). If a subject has disease progression/relapse and a bone marrow aspirate is performed as part of clinical care, bone marrow samples will be collected for correlatives as described in Section 8.6.2 and the laboratory guidelines. Bone marrow samples taken for disease evaluation purposes where MRD is not required to be assessed should still be collected for banking and should include up to 12mL whenever possible.

[14] For subjects with extramedullary plasmacytomas present at the post-induction assessment, PET/CT and/or WB-MRI every 12 weeks during KRd consolidation and for the first year of lenalidomide maintenance, and then once a year for subsequent years (or as clinically indicated).

[15] Approximately 30mL of blood will be collected pre-treatment of every 4 cycles of KRd consolidation (C5D1and C9D1) and D1 of lenalidomide maintenance (if applicable) cycles 1, 3, 5, 7, 9 and 11. An additional blood sample will be collected at progression. See Section 8.6.1 and the laboratory guidelines for detailed information.

[16] Not required for subjects not receiving lenalidomide treatment. For subjects receiving lenalidomide for maintenance, creatinine clearance should be reviewed, and dosing followed per Section 6.3.2.2. If dosing with lenalidomide is delayed due to an extenuating circumstance (e.g., needing a new prescription due to dose reduction), a delay of up to 5 days will not be considered a deviation.

[17] For subjects with serologic evidence of resolved HBV infection (i.e. positive anti-HBs or positive anti-HBc) at Screening. HBV DNA testing must be performed locally. 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. During and following study treatment, subjects who have a history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the study calendar. Results of HBV testing may be reported to the local health authorities.
[18] During the COVID-19 pandemic, virtual visits may be performed per investigator discretion.
[19] Subjects who have permanently discontinued study treatment and have confirmed progression or initiated new anti-cancer treatment will go into Survival Follow-up every 6 months (+/- 30 days) from the date of disease progression or initiation of subsequent anti-cancer treatment until off study criteria in Section 9.2 are met. Survival Follow-up may be conducted via telephone. Any second primary malignancies discovered during the subject's participation in the study will be documented.
[20] For disease evaluation, please refer to footnotes * and II in the IMWG criteria, see Section 13. All response categories require two consecutive assessments, which should be captured in the dataset. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The confirmatory scan data should be entered into the dataset.

8. DETAILS ON STUDY PROCEDURES

Please also refer to the Study Calendars in Section 7.

8.1 Screening Procedures

- **Informed Consent:** No protocol-related assessments may be performed prior to obtaining informed consent.
- **Medical History:** A complete relevant medical history should be obtained, including documentation of any clinically significant pre-existing conditions.
- **Physical Examination and Weight:** Evaluation by body system, including height, weight and neurologic exam to detect peripheral neuropathy.
- **Performance Status:** ECOG performance status
- **Vital Signs:** Vital signs should include temperature, pulse rate, blood pressure and respiratory rate
- **Cardiac Evaluation:** ECG and MUGA or ECHO
- **Forced Expiratory Volume Test:** Subjects with COPD only
- **Laboratory Assessments**
    - Serum chemistries: BUN, creatinine (and calculated creatinine clearance), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
    - CBCD: complete blood count with differential and platelets
    - Serum or urine pregnancy test for FCBP
    - HBV Serology: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody.
    - HBV DNA testing: only for subjects positive for Anti-HBc or Anti-HBs
    - **Blood type and screen:** ABO and Rh blood typing and indirect antiglobulin test to be performed once any time between screening and initiation of study treatment

- **Baseline Symptoms and Toxicities:** Document pre-existing symptoms and any toxicities present (per NCI CTCAEv4.03) at the time of informed consent and prior to the first dose of study treatment
- **Concomitant Medications***:* Document any concomitant medications; concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.
- **Disease Evaluation:**
    - Serum beta2-microglobulin
    - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD**, IgE**), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. **Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.
    - Bone marrow aspirate and biopsy (including MRD analysis/correlatives): If a fresh biopsy is not collected at screening, may use non-decalcified diagnostic tissue (i.e., bone marrow aspirate slides or FFPE tissue) if collected within 6 months of enrollment; see Section 8.6.2.

- Skeletal Survey
- Assess extramedullary plasmacytomas: PET/CT and/or Whole Body (WB)-MRI
  - Note: For subjects who received prior therapy, the skeletal survey or CT will be acceptable and PET/CT/Whole Body MRI is not required

8.2 Induction Procedures

NOTE: The sections below are focused on study procedures, and not drug administration; however, please note that for subjects who completed a pre-study cycle of induction chemotherapy, only 7 cycles of KRdD Induction should be given.
Section 8.2.1 covers the non-laboratory assessments that are to be performed at each study visit.
NOTE: serum or urine pregnancy testing is required weekly only during cycle 1 of induction in FCBP. Thereafter it is required on day 1 of each cycle.

8.2.1 Throughout the Induction Period

- **Physical Exam:** Symptom-directed physical exam only
- **AEs:** Record all AEs per the NCI CTCAEv4.03.
- **Concomitant Medications**: Record any changes in concomitant medications. Concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.
- **Laboratory Assessments**
  - HBV DNA testing: every 12 weeks for up to 6 months after last dose of daratumumab only for subjects positive for Anti-HBc or Anti-HBs at Screening.
- **Disease Evaluation:**
  - Skeletal Survey only if clinically indicated
  - Daratumumab Interference Testing at suspected CR (subjects with IgG Kappa MM only)

8.2.2 Day 1 Cycles 1-8 (unless otherwise noted)

- **Weight:** If a subject's weight changes by more than 20% from induction C1D1, the dose of carfilzomib should be re-calculated.
- **Performance Status:** ECOG performance status
  - **Vital Signs:** Vital signs should include temperature, pulse rate, blood pressure and respiratory rate. For all daratumumab injections, vital signs will be measured per institutional standards but at a minimum prior to the start of injection for all doses. Vital signs at the end of the injection only required for C1D1 and C1D8 and thereafter per Investigator discretion. Subject should remain in clinic for at least 1 hour observation period for the first dose of daratumumab and the first of carfilzomib on study, and per investigator discretion for subsequent doses.
- **Cardiac Evaluation:** ECG
- **Blood type and screen:** ABO and Rh blood typing and indirect antiglobulin test to be performed once any time between screening and initiation of study treatment
- **Laboratory Assessments**
  - Serum chemistries: BUN, creatinine (with calculated creatinine clearance), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH,

albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
    - CBCD: complete blood count with differential and platelets
    - Pregnancy test (serum or urine) in FCBP
- **Disease Evaluation:**
    - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD**, IgE**), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. **Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed for subjects with light chain only disease only and in subjects where at least a CR is suspected or who are maintaining at least a CR. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated.
- **Blood sample for correlatives:** See Study Calendar and Section 8.6.1.
- Per Investigator's discretion, for subjects at higher risk for pulmonary complications that are not hospitalized for monitoring after daratumumab infusion, a follow-up telephone call should be made and documented to monitor their condition within 48 hours (no later than 72 hours) after all daratumumab infusions.

8.2.3 Day 8 Cycles 1-2 Only (unless otherwise noted)

- **Vital Signs:** Vital signs should include temperature, pulse rate, blood pressure and respiratory rate and will be measured per institutional standards but at a minimum prior to the daratumumab injection for all doses. Vital signs at the end of the injection only required on C1D1 and C1D8 and thereafter per Investigator discretion. Subject should remain in clinic for at least 1 hour observation period for the first dose of daratumumab and the first of carfilzomib on study, and per investigator discretion for subsequent doses.
- **Laboratory Assessments**
    - Serum chemistries: BUN, creatinine, glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
    - CBCD: complete blood count with differential and platelets
    - Pregnancy test (serum or urine) in FCBP: Cycle 1 only
- Per Investigator's discretion, for subjects at higher risk for pulmonary complications that are not hospitalized for monitoring after daratumumab infusion, a follow-up telephone call should be made and documented to monitor their condition within 48 hours (no later than 72 hours) after all daratumumab infusions.

8.2.4 Day 15 Cycles 1-8 (unless otherwise noted)

- **Observation:** Observe subject for one hour post daratumumab injection per investigator discretion.
- **Laboratory Assessments**
    - Serum chemistries: BUN, creatinine, glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.

  - CBCD: complete blood count with differential and platelets
  - Pregnancy test (serum or urine) in FCBP: Cycle 1 only
- Per Investigator's discretion, for subjects at higher risk for pulmonary complications that are not hospitalized for monitoring after daratumumab infusion , a follow-up telephone call should be made and documented to monitor their condition within 48 hours (no later than 72 hours) after all daratumumab infusions.

8.2.5 Day 22 Cycles 1-2 Only (unless otherwise noted)

- **Observation:** Observe subject for one hour post daratumumab injection per investigator discretion.
- **Laboratory Assessments**
  - CBCD: complete blood count with differential and platelets
  - Pregnancy test (serum or urine) in FCBP: Cycle 1 only
- Per Investigator's discretion, for subjects at higher risk for pulmonary complications that are not hospitalized for monitoring after daratumumab infusion, a follow-up telephone call should be made and documented to monitor their condition within 48 hours (no later than 72 hours) after all daratumumab infusions.

8.2.6 Post-Induction Disease Evaluation

- **Performance Status:** ECOG performance status
- **Cardiac Evaluation:** ECG
- **Laboratory Assessments**
  - Serum chemistries: BUN, creatinine, glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
  - CBCD: complete blood count with differential and platelets
  - HBV DNA testing: only for subjects positive for Anti-HBc or Anti-HBs at Screening.
- **Disease Evaluation:**
  - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD**, IgE**), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. **Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed in subjects with light chain only disease and in subjects where at least a CR is suspected or who are maintaining at least a CR. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated.
  - Bone marrow aspirate and biopsy for disease evaluation (including MRD analysis/correlatives); see Section 8.6.2 *only those subjects who experience ≥VGPR will undergo an assessment of MRD.
  - Assess extramedullary plasmacytomas: PET/CT and/or WB-MRI
  - Daratumumab Interference Testing at suspected CR (subjects with IgG Kappa MM only)

- **Blood sample for correlatives:** See Study Calendar and Section 8.6.1

8.3 Post-Induction Procedures

Based on disease evaluation after induction, subjects will be divided into 3 separate treatment groups (see Schema 2). The specific post-induction treatments for a given subject differ based on Group, MRD results (based on DNA sequencing) and investigator discretion, but may include: ASCT, KRd consolidation, lenalidomide maintenance and/or observation. Procedures for each category are included in the sections below.

8.3.1 Throughout the Post-Induction Period

- **Physical Exam:** Symptom-directed physical exam only
- **AEs:** Record all AEs per the NCI CTCAEv4.03.
- **Concomitant Medications**: Record any changes in concomitant medications. Concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.
- **Laboratory Assessments**
  - HBV DNA testing: every 12 weeks for up to 6 months after last dose of daratumumab only for subjects positive for Anti-HBc or Anti-HBs at Screening.
- **Disease Evaluation:**
  - Skeletal Survey only if clinically indicated
  - Daratumumab Interference Testing at suspected CR (subjects with IgG Kappa MM only)

8.3.2 ASCT Procedures

8.3.2.1 Stem Cell Mobilization and Collection

All subjects in Group B and subjects in Group A who are transplant eligible will undergo stem cell mobilization and collection (see Section 5.2).

- **AEs:** AEs related to mobilization do not need to be reported. However, any AEs considered related to induction (i.e., either daratumumab, carfilzomib, lenalidomide and/or dexamethasone) should continue to be reported.

8.3.2.2 ASCT

All subjects in Group B will undergo ASCT (see Section 5.4).

- **AEs:** AEs related to HDC and ASCT do not need to be reported. However, any AEs considered related to induction (i.e., either daratumumab, carfilzomib, lenalidomide and/or dexamethasone) should continue to be reported.

8.3.2.3 Post-ASCT Disease Evaluation

- **Performance Status:** ECOG performance status
- **Laboratory Assessments**
  - Serum chemistries: BUN, creatinine, glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total

bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
    - CBCD: complete blood count with differential and platelets
- **Disease Evaluation:**
    - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD**, IgE**), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. **Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed for subjects with light chain only disease and for subjects with a suspected CR or who are maintaining at least a CR. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated.
    - Bone marrow aspirate and biopsy for disease evaluation (including MRD analysis/correlatives); see Section 8.6.2; *only those subjects who experience ≥VGPR will undergo an assessment of MRD.
    - Assess extramedullary plasmacytomas: PET/CT and/or WB-MRI every 12 weeks from the Post-Induction disease evaluation (only subjects with extramedullary plasmacytomas present at the post-induction assessment)
    - Daratumumab Interference Testing at suspected CR (subjects with IgG Kappa MM only)
- **Blood sample for correlatives:** See Study Calendar and Section 8.6.1**.**

8.3.3 KRd Consolidation Procedures

8.3.3.1 Day 1 Cycles 1-12 (unless otherwise noted)

- **Weight:** If a subject's weight changes by more than 20% from KRd consolidation C1D1, the dose of carfilzomib should be re-calculated.
- **Performance Status:** ECOG performance status
- **Cardiac Evaluation:** ECG; Cycles 1, 4, and, if applicable, 7 and 11 (see Disease Evaluation below)
- **Laboratory Assessments**
    - Serum chemistries: BUN, creatinine (with calculated creatinine clearance), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
    - CBCD: complete blood count with differential and platelets
    - Pregnancy test (serum or urine) in FCBP
- **Disease Evaluation:**
    - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD**, IgE**), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. **Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed for subjects with light chain only disease and for subjects with a suspected CR or who are maintaining at least a CR. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated.

- In subjects with ≥VGPR based on blood and urine evaluation, bone marrow aspirate and biopsy; after completion of cycles 4 and 8 only (see Section 8.6.2): A bone marrow aspirate and biopsy will be performed for disease evaluation and to assess MRD/correlatives. Those who convert to MRD (-) per DNA sequencing after cycles 4 or 8 will permanently discontinue KRd. **NOTE:** For those subjects who convert to MRD (-), this evaluation will serve as their post-consolidation disease evaluation (see Section 8.3.3.3).
- Subjects with extramedullary plasmacytomas present at the post-induction assessment: Assess extramedullary plasmacytomas: PET/CT and/or WB-MRI every 12 weeks for a year, then once a year for subsequent years
- Daratumumab Interference Testing at suspected CR (subjects with IgG Kappa MM only)

- **Blood sample for correlatives:** See Study Calendar and Section 8.6.1.

8.3.3.2 Day 15 Cycles 1-12

- **Laboratory Assessments**
  - Serum chemistries: BUN, creatinine, glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
  - CBCD: complete blood count with differential and platelets

8.3.3.3 Post-Consolidation Disease Evaluation

- **Performance Status:** ECOG performance status
- **Cardiac Evaluation:** ECG
- **Laboratory Assessments**
  - Serum chemistries: BUN, creatinine, glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
  - CBCD: complete blood count with differential and platelets
- **Disease Evaluation:**
  Note: For those subjects who permanently discontinue KRd due to conversion to MRD (-) disease via DNA sequencing after completion of cycle 4 or cycle 8, this evaluation will serve as their post-consolidation disease evaluation (see Section 8.3.3.3)
  - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD**, IgE**), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. **Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed for subjects with light chain only disease and for subjects with a suspected CR or who are maintaining at least a CR. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated.

- Bone marrow aspirate and biopsy for disease evaluation (including MRD analysis/correlatives); see Section 8.6.2; *only those subjects who experience ≥VGPR will undergo an assessment of MRD.
- Subjects with extramedullary plasmacytomas present at the post-induction assessment: Assess extramedullary plasmacytomas: PET/CT and/or WB-MRI every 12 weeks for a year, then once a year for subsequent years
- Daratumumab Interference Testing at suspected CR (subjects with IgG Kappa MM only)

8.3.4 Lenalidomide Maintenance Procedures

8.3.4.1 Day 1 Cycles 1-12 (unless otherwise noted)

- **Performance Status:** ECOG performance status
- **Laboratory Assessments**
  - Serum chemistries: BUN, creatinine (with calculated creatinine clearance), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
  - CBCD: complete blood count with differential and platelets
  - Pregnancy test (serum or urine) in FCBP
- **Disease Evaluation:**
  - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD[**], IgE[**]), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. [**]Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed for subjects with light chain only disease and for subjects with a suspected CR or who are maintaining at least a CR. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated.
  - Subjects with extramedullary plasmacytomas present at the post-induction assessment: Assess extramedullary plasmacytomas: PET/CT and/or WB-MRI every 12 weeks for a year, then once a year for subsequent years
  - Daratumumab Interference Testing at suspected CR (subjects with IgG Kappa MM only)
- **Blood sample for correlatives:** See Study Calendar and Section 8.6.1.

8.3.4.2 At6and 12 months after post-induction (Group A) or post-consolidation (Groups B and C) and then annually (+/- 30 days) until disease progression or initiation of new anti-cancer treatment:

:

- Bone marrow aspirate and biopsy for disease evaluation and MRD analysis/correlatives; see Section 8.6.2; *only those subjects who experience ≥VGPR will undergo an assessment of MRD.
- For subjects in Group B who convert to MRD (-) after ASCT and do not receive consolidation, bone marrow aspirate and biopsy for disease evaluation and MRD analysis/correlatives should be evaluated at 6 and 12 months after transplant.

8.3.4.3 Day 1 every 3 Cycles for Cycles 13+ (unless otherwise noted)

- **Performance Status:** ECOG performance status
- **Laboratory Assessments**
  - Serum chemistries: BUN, creatinine (with calculated creatinine clearance), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
  - CBCD: complete blood count with differential and platelets
  - Pregnancy test (serum or urine) in FCBP: D1 of every cycle.
- **Disease Evaluation:**
  - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD**, IgE**), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. **Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed for subjects with light chain only disease and for subjects with a suspected CR or who are maintaining at least a CR. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated.
  - Subjects with extramedullary plasmacytomas present at the post-induction assessment: Assess extramedullary plasmacytomas: PET/CT and/or WB-MRI every 12 weeks for a year, then once a year for subsequent years
  - Daratumumab Interference Testing at suspected CR (subjects with IgG Kappa MM only)

8.4 Safety Follow-up Visit

This visit should occur in subjects 30 days (+/-10 days) after study treatment stops for whatever reason (toxicity, progression, or at discretion of the investigator). **NOTE:** this 30-day time period applies even if the subject is taken off study treatment and begins new anti-cancer treatment during this time period.

For subjects in Group A who do not go on lenalidomide maintenance, this visit may occur the day of (but prior to) stem cell mobilization (if the subject is eligible for transplant). For subjects in Group B who do not go on lenalidomide maintenance after ASCT, this visit may occur the day of the post-ASCT disease evaluation.

- **Performance Status:** ECOG performance status
- **Laboratory Assessments**
  - Serum chemistries: BUN, creatinine, glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
  - Hematology: complete blood count with differential and platelets
- **AEs:** Record all AEs; subjects who have ongoing Grade 4 AE or SAE at the time of discontinuation from treatment, and those who come off treatment prematurely for safety

reasons will continue to be followed until the event is resolved or deemed irreversible by the investigator.

- **Concomitant Medications**: Record any changes in concomitant medications. Concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.

8.5 Follow-up

Any second primary malignancies discovered during long-term follow-up will be documented.

PFS Follow-up: For subjects who permanently discontinue study treatment before relapse or PD (including subjects who do not go on lenalidomide maintenance), disease evaluations should continue to be performed per standard of care until relapse or confirmed PD, start of a new anticancer treatment, or the subject meets the criteria for Off Study as defined in Section 9.2, whichever occurs first.

Survival Follow-up: For subjects who have had confirmed disease progression or started new anticancer treatment, long-term follow-up contact will occur every 6 months (+/- 30 days) from the date of confirmed disease progression or initiation of new anti-cancer treatment until the subject meets the criteria for Off Study as defined in Section 9.2 and may be conducted via telephone. Follow-up clinical information may also be obtained through chart reviews or other data sources (e.g. death registries).

The investigator is responsible for following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care and is being treated at another institution.

If the subject cannot be contacted following three attempted telephone calls over a period of 10 business days, the subject will be contacted in writing. Lost to follow-up is defined as four consecutive unsuccessful documented attempts (telephone and written) to contact the subject.

NOTE: in the event the criteria for the final analysis are met, and there are subjects who have not yet been permanently discontinued from study treatment, subjects in follow-up will continue to be followed until all subjects have permanently discontinued study treatment and completed the Safety Follow-up Visit (see above).

8.6 Biospecimen Correlative Studies

8.6.1 Blood Samples

Correlatives: Approximately 30 mL of blood will be collected at each time-point for correlatives as outlined in the Study Calendars in Section 7. The blood will be used for peripheral blood phenotyping by flow cytometry, and for PBMC isolation (T cell receptor sequencing) and plasma collection (cytokine profiling). Comprehensive peripheral immune profiling techniques will be employed including:

- Soluble immune analytes measurements combining cytokine, chemokine and growth factor profiling [15 cytokines (IL-1b. IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12p70,

IL-13, IL-15, IL-17, IL-22, TNFa, INFg); 5 chemokines (IL-8, MIP1a, MIP1b, MCP1, IP10); and 5 growth factors (VEGF, FGF, PDGF, EGF, HGF) together with 3 markers of hypoxia and bone remodeling (IGF-1, HIF, RANK-L)].

- Flow cytometry-based enumeration and characterization of circulating effector and functional memory T cell mobilization (T helper and cytotoxic T cell subsets) [24] as well as γδ T cells, NK cells, and inducible NK-T activation [24,25]
- Circulating T cells (αβ and γδ subsets) clonal expansion assessment TCR-VD(J) rearrangement sequencing.

8.6.2 Bone Marrow Samples

In addition to the bone marrow samples required for routine clinical disease evaluation, bone marrow samples from aspirates and biopsies performed after each phase of treatment as applicable (induction, ASCT, consolidation with KRd, maintenance) will also be evaluated for:

- Flow cytometry-based tumor microenvironment analysis: MRD status will be assessed for this study in part using a flow cytometry-based MM MRD assay developed by the Euroflow consortium (https://www.ncbi.nlm.nih.gov/pubmed/28104919) utilizing 10 markers (CD138, CD38, CD45, CD19 CD56, CD27, CD117, CD81, κ / λ free light chains) to identify plasma cells, differentiate normal from MM-PC and well as PC clonality. Using alternative gating strategy, this flow cytometry panel will also allow identification and characterization of NK, T, B and myeloid cell subsets. MRD flow will not be required at screening.
- MRD assessment by NGS: MRD will be assessed via NGS which utilizes MM cell DNA from bone marrow samples.
- Micro-array / global gene expression analysis of isolated plasma cells.
- Clonal evolution of PC (and MM-PC subpopulation) IgG VJ rearrangement sequencing.

For Group A subjects on lenalidomide maintenance or PFS follow up ,bone marrow aspirate and biopsy will be performed post-induction at the time-points indicated in the Study Calendar. For Group B and C subjects with ≥VGPR based on blood and urine evaluation, bone marrow aspirate and biopsy will also be performed after completion of cycle 4 and cycle 8 (if applicable) of KRd consolidation for disease evaluation and MRD status via flow cytometry and NGS. In addition, bone marrow aspirate will be collected for banking/correlatives at disease progression/relapse as indicated below if a bone marrow aspirate is performed as part of clinical care.

In addition to the volumes required for routine clinical evaluation, a minimum of 15mL of bone marrow aspirate (1st pull or 1st technical pull after needle repositioning) will be required for MRD assessment by flow cytometry and NGS and banking. See laboratory guidelines for details. In the event difficulty arises while marrow specimens are collected preventing collection of all 5x3ml of bone marrow aspirate, the sample should be prioritized as follows:

1) MRD NGS (Adaptive):3ml
2) MRD flow (Immune Monitoring Core Lab): 6ml
3) Banking (Hematology Oncology Translational Lab): 6ml. Optional: If possible, an additional 6ml of bone marrow aspirate can be collected at baseline and upon progression/relapse for banking [i.e. $CD138^+$ plasma cell isolation (B cell receptor sequencing)]. Note: if a bone marrow biopsy/aspirate is done for disease evaluation

purposes where MRD is not required to be assessed due to disease response, bone marrow should still be collected for banking and should include up to 12ml whenever possible.

9. DISCONTINUATION FROM TREATMENT AND STUDY WITHDRAWAL

9.1 Treatment Discontinuation Criteria

Study treatment will continue until one of the following criteria applies:

- Disease relapse or progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw study consent
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator
- Study subject becomes pregnant
- Completion of protocol-directed therapy per Investigator-discretion (e.g. MRD negative subjects entering observation per Investigator)

NOTE: In the event the criteria for the final analysis are met, and there are subjects who have not yet been permanently discontinued from study treatment, they will continue to receive treatment until one of the above criteria applies.

9.2 Off Study

Subjects will remain on study until the criteria for the final analysis are met (Section 14.5.1). Reasons a subject may be removed from study early include, but are not limited to:

- Subject non-compliance with study participation, in the opinion of the investigator
- The subject or legal representative (such as a parent or legal guardian) withdraws study consent
- The subject is lost to follow-up
- Study completion
- Investigator's decision to withdraw the subject
- Subject death
- Early study termination

When subjects are removed from the study, the reason for study removal and date the subject was removed should be documented.

Subjects that are Off Study will not participate in any study related procedures, including data collection.

10. DRUG INFORMATION

10.1 Daratumumab

For complete information, please refer to the latest version of the daratumumab IB, provided as a document separate from this protocol. Please also refer to the latest version of the prescribing information for daratumumab, which can be found at http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf

Daratumumab is a CD38-directed cytolytic antibody approved by the FDA in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. It is also approved as monotherapy for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an IMiD agent or who are double refractory to both of these classes of drugs.

10.1.1 Supplier/How Supplied?

Daratumumab will be supplied free of charge to study subjects by Janssen Biotech, Inc., the manufacturer of daratumumab.

For SC injections, Daratumumab will be provided as a fixed-dose (1800 mg), combination drug product containing rHuPH20 drug substance (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.

10.1.2 Preparation

NOTE: See latest version of the daratumumab prescribing information which can be found at http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf for the most up to date information on preparation of daratumumab for administration.

10.1.3 Storage and Stability

All investigational study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and will be inaccessible to unauthorized personnel.

Store Daratumumab for subcutaneous injection vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.
Daratumumab prepared for SC administration should be used immediately. If not used immediately, store solution for up to 4 hours at ambient temperature and ambient light. Discard after 4 hours, if not used.

10.1.4 Handling

Daratumumab should be handled using standard precautions for the safe handling of antineoplastic agents. Personal protection equipment is recommended. It must be dispensed only from official study sites by authorized personnel according to local regulations and stored in a

secure area according to local regulations. It is the responsibility of the investigator to ensure that study drug is only dispensed to eligible study subjects.

10.1.5 Accountability

An adequate record of receipt, distribution, destruction, or return of this agent must be kept in the form of a Drug Accountability Form. The investigator, or responsible party designated by the investigator, will maintain a careful record of the inventory using the Drug Accountability Form**.** The investigational drug for this clinical trial shall only be dispensed by authorized personnel to subjects enrolled in this clinical trial.

10.1.6 Destruction

The investigator or designee is responsible for keeping accurate records of the clinical supplies received from Janssen Biotech Inc., including the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused product will be destroyed at the site according to site pharmacy policies or as dictated by the manufacturer. Any vials that are used during dose preparation may be destroyed immediately after preparation. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.1.7 Adverse Events Associated with Daratumumab SC

The most frequently reported adverse reactions in clinical trials were: infusion related reactions, upper respiratory tract infection, bronchitis, pneumonia, thrombocytopenia, anemia, neutropenia, anorexia, peripheral sensory neuropathy, headache, hypertension, cough, dyspnea, constipation, diarrhea, nausea, vomiting, muscle spasms, peripheral edema, asthenia, pyrexia, back pain, insomnia, and arthralgia. Also common were: urinary tract infection, flu like symptoms, herpes zoster, sepsis, hyperglycemia, hypocalcemia, dehydration, arrhythmia, chills, low oxygen saturation, pharyngitis, pulmonary edema, dizziness, pancreatitis, rash, pruritis, muscular chest pain.

The most commonly reported adverse events from recombinant human hyaluronidase (rHuPH20, enzyme included in daratumumab SC) when injected beneath the skin have been mild injection site reactions, such as redness, pain, bruising, itching, burning, tenderness, swelling, hardness, irritation, tingling, numbness, and rash. Mild to moderate headache have also been reported. Some patients who receive rHuPH20 may develop antibodies directed to the PH20 hyaluronidase; approximately 5% of the general population has these antibodies even without ever having been exposed to rHuPH20.

See Section 1.3 and the daratumumab Investigator's Brochure for additional information. See Section 1.3.3.3 for safety information when daratumumab was evaluated in combination with carfilzomib, lenalidomide and dexamethasone.

The following warnings are associated with the use of daratumumab SC (from the current prescribing information):

- **Hypersensitivity and Other Administration Reactions:** Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO. **SYSTEMIC REACTIONS:** In a pooled safety population of 490 patients who received DARZALEX FASPRO as monotherapy or in combination, 11% of patients experienced a systemic administration-related reaction (Grade 2: 3.9%, Grade 3: 1.4%). Systemic administration-related reactions occurred in 10% of patients with the first injection, 0.2% with the second injection, and cumulatively 0.8% with subsequent injections. The median time to onset was 3.7 hours (range: 9 minutes to 3.5 days). Of the 84 systemic administration-related reactions that occurred in 52 patients, 73 (87%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in less than 1% of the patients. Severe reactions included hypoxia, dyspnea, hypertension,tachycardia, choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. **LOCAL REACTIONS:** In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.6%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 7 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO.
- **Neutropenia**: Daratumumab may increase neutropenia induced by background therapy.
- **Thrombocytopenia:** Daratumumab may increase thrombocytopenia induced by background therapy.
- **Embryo-Fetal Toxicity:** Can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception.
- **Interference** with cross-matching and red blood cell antibody screening.

10.2 Carfilzomib

For complete information, please refer to the latest version of the prescribing information for carfilzomib, which can be found at www.kyprolis.com.

Carfilzomib is proteasome inhibitor approved by the FDA in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy, or as monotherapy in patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

10.2.1 Supplier/How Supplied

Carfilzomib will be supplied free of charge to study subjects by Amgen, the manufacturer of carfilzomib. The vial size it will be provided in is 60 mg and will be labeled “Carfilzomib for injection 60mg/vial in 4x carton”. Carfilzomib will be provided as a lyophilized powder which, when reconstituted, contains a 2 mg/mL isotonic solution of carfilzomib.

10.2.2 Reconstitution and Preparation

Refer to the latest version of the prescribing information for carfilzomib, which can be found at www.kyprolis.com, for instructions on reconstitution and preparation of carfilzomib.

10.2.3 Storage and Stability

Refer to the latest version of the prescribing information for carfilzomib, which can be found at www.kyprolis.com, for details on stability of unopened vials of carfilzomib, and on stability of carfilzomib once it is reconstituted.

10.2.4 Handling

Carfilzomib should be handled using standard precautions for the safe handling of antineoplastic agents. Personal protection equipment is recommended. It must be dispensed only from official study sites by authorized personnel according to local regulations and stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that study drug is only dispensed to eligible study subjects.

10.2.5 Accountability

An adequate record of receipt, distribution, destruction, or return of this agent must be kept in the form of a Drug Accountability Form. The investigator, or responsible party designated by the investigator, will maintain a careful record of the inventory using the Drug Accountability Form**.** The investigational drug for this clinical trial shall only be dispensed by authorized personnel to subjects enrolled in this clinical trial.

10.2.6 Destruction

The investigator or designee is responsible for keeping accurate records of the clinical supplies received from Amgen Inc., including the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused product will be destroyed at the site according to site pharmacy policies or as dictated by the manufacturer. Any vials that are used during dose preparation may be destroyed immediately after preparation. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.2.7 Adverse Events Associated with Carfilzomib

For complete information on safety, please refer to the latest version of the prescribing information for carfilzomib, which can be found at www.kyprolis.com.

See Section 1.3.3.3 for safety information when carfilzomib was evaluated in combination with daratumumab, lenalidomide and dexamethasone.

The safety of carfilzomib in combination with lenalidomide and dexamethasone (KRd) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. Adverse Reactions that occurred at a rate of ≥10% in the KRd arm (n=392) during the first 12 cycles of therapy are in the table below.

	KRd Arm n (%)	
Adverse Reaction	**Any Grade**	**≥ Grade 3**
Anemia	138 (35)	53 (14)
Asthenia	53 (14)	11 (3)
Bronchitis	54 (14)	5 (1)
Constipation	68 (17)	0
Cough	91 (23)	2 (1)
Diarrhea	115 (29)	7 (2)
Dyspnea	70 (18)	9 (2)
Fatigue	109 (28)	21 (5)
Hyperglycemia	43 (11)	18 (5)
Hypertension	41 (11)	12 (3)
Hypocalcemia	55 (14)	10 (3)
Hypokalemia	78 (20)	22 (6)
Insomnia	63 (16)	6 (2)
Muscle spasms	88 (22)	3 (1)
Nasopharyngitis	63 (16)	0
Nausea	60 (15)	1 (0)
Neutropenia	124 (32)	104 (27)
Peripheral edema	63 (16)	2 (1)
Peripheral neuropathies	43 (11)	7 (2)
Pneumonia	54 (14)	35 (9)
Pyrexia	93 (24)	5 (1)
Rash	45 (12)	5 (1)
Thrombocytopenia	100 (26)	58 (15)
Upper Respiratory Tract Infection	85 (22)	7 (2)
Venous Embolic and Thrombotic Events	49 (13)	16 (4)

Laboratory abnormalities ≥ Grade 3 reported at a rate of ≥ 10% in the KRd arm included decreases in the following (% of patients): lymphocytes (46%), ANC (39%), phosphorus (31%), platelets (26%), total WBC (25%), hemoglobin (15%) and potassium (11%).

The following warnings are associated with the use of carfilzomib (from the August 2020 prescribing information):

The most common adverse reactions occurring in at least 20% of patients treated with Kyprolis in the combination therapy trials: anemia, diarrhea, fatigue, hypertension, pyrexia, upper respiratory tract infection, thrombocytopenia, cough, dyspnea, and insomnia.

Other risks of special concern include: cardiac toxicities, acute renal failure, Tumor Lysis Syndrome (TLS), pulmonary toxicity including (acute respiratory distress syndrome, acute respiratory failure, acute diffuse infiltrative pulmonary disease), pulmonary hypertension, dyspnea, hypertension including hypertensive crisis, venous thrombosis, infusion-related

reactions, hemorrhage, thrombocytopenia, hepatic toxicity and hepatic failure, Hepatitis B reactivation, thrombotic microangiopathy, Posterior Reversible Encephalopathy Syndrome (PRES), Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients and embryo-fetal toxicity.

Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients treated with carfilzomib who have had prior or concurrent immunosuppressive therapy. The causal relationship with carfilzomib is unknown. 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. If PML is suspected, Carfilzomib should be HELD and patients promptly referred to a specialist with appropriate diagnostic testing initiated. Discontinue carfilzomib if PML diagnosis is confirmed.

10.3 Lenalidomide

For complete information, please refer to the latest version of the prescribing information for lenalidomide, which can be found at www.revlimid.com.

Lenalidomide is a thalidomide analogue approved by the FDA in combination with dexamethasone for the treatment of patients with MM, and for use as maintenance therapy post ASCT.

10.3.1 Supplier/How Supplied

Lenalidomide will be supplied free of charge to study subjects by Celgene Corporation, the manufacturer of lenalidomide, through a contract pharmacy. Subjects in the U.S. must be enrolled into the REVLIMID Risk Evaluation and Mitigation Strategy (REMS)™ program for the procurement of lenalidomide. Lenalidomide is formulated in hard capsules containing 2.5 mg, 5 mg, 10 mg, 15 mg, or 25 mg active drug for PO administration only.

Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Further information about the Revlimid REMS® program is available at www.celgeneriskmanagement.com.

10.3.2 Storage and Stability

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

10.3.3 Handling

Lenalidomide should be handled using standard precautions for the safe handling of antineoplastic agents. Personal protection equipment is recommended. Lenalidomide capsules should not be opened or broken. It is the responsibility of the investigator to ensure that study drug is only dispensed to eligible study subjects.

10.3.4 Administration Compliance

For subjects due for another cycle of lenalidomide and have a visit scheduled at the research site, lenalidomide will be dispensed to subjects, and the study drug pill bottles returned to site research staff. Local pharmacy staff will report the number of capsules in the study drug bottles returned to site research staff. The number of capsules taken by the subject per cycle will be derived from these capsule counts rather than reported by the subjects on a pill diary. Subjects will be asked to return used study drug bottles at designated time-points.
For subjects due for another cycle of lenalidomide and do not have a visit scheduled at the research site, lenalidomide may be shipped to the subject's home after approval of the sponsor. Administration will be documented using a diary or other source documentation of lenalidomide administration at home rather than a pill count. Pill bottles will not be returned to the site research staff.

Compliance with study treatment will be assessed at the end of each cycle. Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol. At the discretion of the investigator, a subject may be permanently discontinued from the protocol for non-compliance with study drug.

10.3.5 Accountability

An adequate record of receipt, distribution, destruction, or return of this agent must be kept in the form of a Drug Accountability Form. The investigator, or responsible party designated by the investigator, will maintain a careful record of the inventory using the Drug Accountability Form**.** The investigational drug for this clinical trial shall only be dispensed by authorized personnel to subjects enrolled in this clinical trial.

10.3.6 Destruction

The investigator or designee is responsible for keeping accurate records of the clinical supplies received from Celgene Corporation, including the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused product will be destroyed (after the appropriate steps have been taken to count and document the number of units returned) at the site according to site pharmacy policies or as dictated by the manufacturer. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.3.7 Adverse Events Associated with Lenalidomide

For complete information on safety, please refer to the latest version of the prescribing information for lenalidomide, which can be found at www.revlimid.com. The most common adverse reactions (≥20%) when lenalidomide is used in MM include diarrhea, fatigue, anemia, constipation, neutropenia, leukopenia, peripheral edema, insomnia, muscle cramp/spasms, abdominal pain, back pain, nausea, asthenia, pyrexia, upper respiratory tract infection, bronchitis, nasopharyngitis, gastroenteritis, cough, rash, dyspnea, dizziness, decreased appetite, thrombocytopenia and tremor.

See Section 1.3.3.3 for safety information when lenalidomide was evaluated in combination with daratumumab, carfilzomib and dexamethasone when used as maintenance.

The following warnings are associated with the use of lenalidomide **in MM** (from the October 2019 prescribing information; Black Box Warnings are noted as such):

- **BLACK BOX WARNING: Embryo-fetal Toxicity**: 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 embryo-fetal death. Because of this, lenalidomide is only available through a restricted distribution program called the REVLIMID REMS™ program.
- **BLACK BOX WARNING: Hematologic Toxicity:** Lenalidomide can cause significant neutropenia and thrombocytopenia.
- **BLACK BOX WARNING: Venous and Arterial Thromboembolism:** There is a significantly increased risk of deep vein thrombosis and pulmonary embolism, as well as risk of myocardial infarction and stroke in patients with MM receiving lenalidomide in combination with dexamethasone. Anti-thrombotic prophylaxis is recommended. **Second Primary Malignancies:** In clinical trials in patients with MM receiving lenalidomide an increase of invasive second primary malignancies notably AML and MDS have been observed. The increase of cases of AML and MDS occurred predominantly in NDMM patients receiving lenalidomide in combination with oral melphalan (frequency of 5.3%) or immediately following high dose intravenous melphalan and ASCT (frequency of up to 5.2%).
- **Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of patients with MM and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors.).
- **Allergic Reactions, including fatalities**: Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal.
- **Tumor Lysis Syndrome:** Fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment.
- **Impaired Stem Cell mobilization**: A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with lenalidomide has been reported.

The most common adverse reactions include: leukopenia, neutropenia, febrile neutropenia, granulocytopenia, lymphopenia, anemia, thrombocytopenia, vision blurred, diarrhea, abdominal pain, constipation, dyspepsia, nausea, vomiting, asthenia, fatigue, edema, peripheral edema, pyrexia, chills, pneumonia, influenza, bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, gastroenteritis, renal failure, nasopharyngitis, pharyngitis rhinitis, weight loss, decreased appetite, hyperglycemia, hypokalemia, hypocalcemia, alanine aminotransferase increased, gamma-glutamyltransferase increased, arthralgia, back pain, bone pain, muscle

spasms, myalgia, tumor flare dizziness, dysgeusia, headache, cataract, paresthesia, hypoesthesia, neuropathy, peripheral neuropathy, tremor, cough, dyspnea, epistaxis, pulmonary embolism, deep vein thrombosis, pruritus, rash, depression, insomnia.

10.4 Dexamethasone

Dexamethasone is a synthetic adrenoglucocorticoid. It is commercially available as a generic in tablet form for oral administration. It is indicated for a variety of medical conditions, including cancer. Commercial supplies of dexamethasone will be used for this study and charged to study subjects or their insurance company.

10.4.1 Storage

Dexamethasone is to be stored at controlled room temperature 20 to 25°C (68 to 77°F). Consult the package insert of the respective product for additional storage and usage instructions.

10.4.2 Summary of Adverse Events Associated with Dexamethasone

See Reference [27] for a more complete summary. Also see Section 6.4.2, Table 15.

The side effects from systemic glucocorticoids are usually dose and duration dependent and can impact virtually all body systems. Common side effects include thinning of the skin, purpura, Cushingoid appearance, weight gain, sleep disturbance and mood changes. Hyperglycemia is common if these agents are used in patients with pre-existing diabetes or those at risk of diabetes for other reasons. Cataracts are also common with prolonged (>1 year) of glucocorticoids. Other risks of concern with glucocorticoids include an increased risk of cardiovascular disease and hypertension (particularly when glucocorticoids are prescribed in patients with pre-existing cardiac or renal disease), increased risk of peptic ulcer disease and gastritis (especially when patients are also taking nonsteroidal anti-inflammatory agents), osteoporosis, increased fracture risk, osteonecrosis, myopathy, edema, and immunosuppression with an increased risk of infection. With the exception of cataracts and some of the cardiac and bone toxicities, adverse effects from glucocorticoids are at least partially reversible upon discontinuation.

11. DATA AND SAFETY MONITORING PLANS

Data will be collected in electronic case report forms (eCRFs). Study personnel will be trained on data entry by the sponsor and provided protocol-specific eCRF guidelines.

This protocol will be monitored according to the processes in effect for all LCI investigator-initiated studies, the protocol-specific monitoring plan, and will abide by applicable regulations and guidelines (e.g. Good Clinical Practice [GCP]). It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator and other sponsor-level team members will meet regularly to monitor subject consents, enrollment and retention, safety data, and timeliness/validity/integrity of the data. Documentation of these meetings will be kept with study records. The Sponsor-Investigator will submit reports to the LCI Data and Safety Monitoring Committee according to the institutional Data and Safety Monitoring Plan.

This study will be monitored to ensure the study is conducted in compliance with the study protocol, SOPs of the LCI and Atrium Health Office of Clinical and Translational Research (and/or other participating institutional SOPs), the FDA, and other applicable regulations and guidelines (e.g. GCP).

12. ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

12.1 Definitions

12.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a study subject who is administered any drug that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials are also considered adverse events. Adverse events may also include pre or post-treatment complications that occur as a result of protocol mandated procedures (e.g., invasive procedures such as biopsies).

An increase in grade to a pre-existing CTCAE toxicity grade present at the time of study treatment initiation will be recorded as an AE. Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an AE if they are judged clinically significant by the investigator and/or require a medical intervention or dose modification.

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study treatment administration should be considered pre-existing and should be documented.

An AE does not include:

- relapse or progression of the underlying malignant disease;
- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); **NOTE:** the condition that leads to the procedure may be an adverse event;
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions);
- overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation

The severity of adverse events should be classified and recorded according to the CTCAE version 4.03.

12.1.2 Adverse Event of Special Interest (AESI)

Adverse Events of Special Interest (AESI) that require expedited reporting to Janssen Scientific Affairs, LLC for subjects exposed to daratumumab include:

- Infusion Reactions ≥ Grade 3
- Infections ≥ Grade 4
- Cytopenias ≥Grade 4
- HBV Reactivation
- Other malignancies

12.1.3 Special Reporting Situations for Daratumumab

Safety events of interest for daratumumab that requires expedited reporting and/or safety evaluating include, but are not limited to:

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

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 AEs.

12.1.4 Special Reporting Situations for Lenalidomide

Important safety information to be reported for lenalidomide, includes, for example:

- any SAE, pregnancy or secondary primary malignancies not previously reported as referenced in Section 12.3
- Adverse Events occurring during breastfeeding
- lack of therapeutic efficacy for lenalidomide*
- suspected transmission of infectious agents
- medication errors
- overdose
- abuse
- misuse
- off-label use which is not in conformity with the Protocol
- occupational exposure
- any public health emergency
- any major safety finding arising from an audit or a Regulatory Authority inspection and

- any issue which may affect the conduct of the Study, the safety of Study subjects or the risk/benefit ratio of lenalidomide

* "Lack of therapeutic efficacy" is defined as a significant failure of lenalidomide to achieve an expected pharmacologic or therapeutic outcome for an indication approved under the marketing authorization.

Overdose

Overdose for lenalidomide, as defined for this protocol, refers to lenalidomide dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of lenalidomide assigned to a given subject, regardless of any associated adverse events or sequelae.

PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose
SC	10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Avenue
Summit, NJ 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

12.1.5 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the Sponsor-Investigator could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

12.1.6 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

12.1.7 Serious AE or SAR

An AE or SAR is to be considered serious if the investigator deems it as such and the event results in any of the following outcomes:

- Death (fatal);
- Life-threatening situation (subject is at immediate risk of death);
- Persistent or significant disability/incapacity;
- Requires or prolongs inpatient hospitalization*;
- A congenital anomaly/birth defect in the offspring of a subject who received study drug;
- Is a suspected transmission of any infectious agent via a medicinal product;
- Based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the afore listed outcomes from occurring (e.g. intensive treatment in an emergency room without hospitalization, blood dyscrasias or convulsions that do not result in hospitalization, development of drug dependency or drug abuse).

<u>NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.</u>

<u>Pregnancy and Lactation Exposure</u>
The following do not meet the criteria for seriousness per ICH definition but must be reported in the same manner as SAEs. Therefore, these events are considered serious for reporting purposes:

- Lactation exposure within 90 days of the subject's last dose of daratumumab and 30 days after last dose of all other study drugs.
- Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study treatment, or within 90 days after last dose of daratumumab and 30 days after last dose all other study drugs.
    - Pregnancies in partners of male subjects exposed to daratumumab. Informed consent of the pregnant partner will be required prior to reporting health information on a pregnant partner.

*Hospitalizations for study drug administration, protocol-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events, will not be recorded as SAEs. Other hospitalizations planned at the beginning of the trial also do not need to be reported as an SAE.

12.1.7.1 Serious Adverse Drug Reaction (SADR)

A serious adverse drug reaction is a serious adverse event (SAE) that is considered to at least have a reasonable possibility of a causal relationship, based on facts and evidence, between the study drug and the AE.

12.1.7.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected Serious Adverse Reaction (SUSAR) is a Serious Adverse Drug Reaction (SADR) that is unexpected (as defined in Section 12.1.8).

12.1.7.3 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.]

12.1.7.4 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.

12.1.8 Unexpected AE (AE or SAE) or SAR

An AE or SAR (whether serious or not) is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DARZALEX+Faspro-pi.pdf

For DARZALEX® (daratumumab), the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

12.1.9 Product Quality Complaint (PQC) for Daratumumab

A product quality compliant is defined as any suspicion of a daratumumab 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

12.1.10 Unanticipated Problem (UAP)

An UAP is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g., IB, informed consent) and the study population characteristics that is related or possibly related to participation in the research study and places the participant at an increased risk. By this definition, any event that meets the criteria defined in Section 12.1.8 would meet the criteria for a UAP. However other events may also meet the criteria for a UAP, e.g., a lost or stolen laptop computer that contains sensitive study information.

12.2 Attribution

The relationship to study treatment should be assessed using the following definitions:

Definite	The AE is ***clearly related*** to the drug(s) under investigation
Probable	The AE is ***likely related*** to the drug(s) under investigation
Possible	The AE ***possibly related*** to the drug(s) under investigation
Unlikely	The AE is ***doubtfully related*** to the drug(s) under investigation
Unrelated	The AE is ***clearly not related*** to the drug(s) under investigation

The investigator is responsible for verifying and providing source documentation for all AEs and assigning the attribution for each event for all subjects enrolled on the trial.

12.3 Timing and Reporting

12.3.1 Adverse Events

All AEs, from the time of study treatment initiation until 30 days after last dose of study treatment (including event name, grade, start/stop date and attribution) will be documented.

12.3.1.1 Reporting to Sponsor-Investigator

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout). For any other experience or condition that meets the definition of an SAE, AESI, or Special Reporting Situation, recording of the event must begin from day 1 of treatment and continue through 30 days after last dose of study treatment. All SAEs and AESIs (whether considered related or not, expected or not) must be reported to the Sponsor-Investigator within 1 business day of awareness. Special Reporting Situations must be recorded in the eCRF with an email notification to the Sponsor-Investigator or designee within 1 business day of awareness. SAEs that are determined to be related to study treatment or procedures must be reported to the Sponsor-Investigator throughout the duration of the subject's participation in the trial (from consent until off-study).

When new significant information becomes available, a follow-up report must be reported to the Sponsor-Investigator within 1 business day of awareness.

All serious adverse events 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)

It is the responsibility of the Sponsor-Investigator, investigators and the protocol team to ensure SAEs are reported according to the Code of Federal Regulations (CFR), GCP, the protocol guidelines, IRB, and FDA policy.

12.3.1.2 Reporting to Janssen Scientific Affairs, LLC

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

- Electronically via Janssen SECURE Email service (preferred) to IIS-BIO-VIRO-GCO@its.jnj.com
- For business continuity purposes, if SECURE Email is non-functional:
    - Facsimile (fax) to 866-651-0219, receipt of which is evidenced in a successful fax transmission report
- Telephone to current Local Trial Manager (if fax is non-functional).

12.3.1.2.1 SAEs for Daratumumab

From the time of initiation of study treatment, through 30 days after the last dose of study treatment, all SAEs (whether considered related or not, expected or not, and including any Special Reporting Situation or PQCs for daratumumab that meet the criteria of an SAE [see Sections 12.1.3]) excluding those from subjects not exposed to daratumumab must be reported to Janssen Scientific Affairs, LLC by the Sponsor-Investigator or designee within 24 hours of awareness of the event.

12.3.1.2.2 AESI for Daratumumab

AESI for daratumumab (see Section 12.1.2) will be reported from the time of study treatment initiation to 30 days after last dose to Janssen Scientific Affairs, LLC by the Sponsor-Investigator or designee within 24 hours of Sponsor-Investigator awareness.

12.3.1.2.3 PQC for Daratumumab

A PQC for daratumumab (see Section 12.1.9) 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 subjects, 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 daratumumab must be reported to Janssen Scientific Affairs, LLC by the Sponsor-Investigator or designee within 24 hours after being made aware of the event. An email to this effect should be sent to IIS-BIO-VIRO-GCO@its.jnj.com and depending on the nature of the complaint 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 Sponsor-Investigator must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timeline. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor 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 Sponsor-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.

12.3.1.2.4 Special Reporting Situations for Daratumumab

Any Special Reporting Situation for daratumumab from the time of consent until 30 days after last dose of daratumumab will be documented.

Any Special Reporting Situation for daratumumab (see Section12.1.3) will be reported to Janssen Scientific Affairs, LLC by the Sponsor-Investigator or designee within 24 hours of Sponsor-Investigator awareness.

12.3.1.2.5 Pregnancy

All initial reports of pregnancy must be reported as an SAE to Janssen Scientific Affairs, LLC by the Sponsor-Investigator or designee within 24 hours of becoming aware of the event. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered SAEs and must be reported as such.

Any subject who becomes pregnant during study treatment must promptly discontinue further study treatment.

Because the effect of daratumumab on sperm is unknown, pregnancies in partners of male subjects exposed to daratumumab will be reported by the Sponsor-Investigator or designee within 24 hours of becoming aware of the event as an SAE. 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.

12.3.1.2.6 Individual Case Safety Report (ICSR)

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

Maintenance of Safety Information
All safety data should be maintained in a clinical database in a retrievable format. The Sponsor-Investigator will 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's request.

12.3.1.3 Reporting to Amgen

All SUSARs and Pregnancy and Lactation Exposure Reports generated from the Study will be reported on a MedWatch form. To avoid misinterpretation, all SUSARs reports provided must clearly indicate the reported AE terms, seriousness criterion, reported assessment of causality and Sponsor assessment of causality (if different).

Sponsor will inform Amgen of any pregnancy occurring and/or existing during exposure to carfilzomib and potential infant exposure within 10 calendar days of Sponsor awareness. Amgen may in accordance with local data privacy laws request the subject's physician's contact information in order to follow-up the pregnancy until birth outcome.

SUSARs will be submitted to Amgen on a MedWatch form within twenty-four (24) hours of submitting that report to the applicable regulatory authority.

Additional information should be sought on initial and/or follow-up SAE reports and Pregnancy and Lactation Exposure Reports with incomplete information. The information obtained from the report source should be sufficient to provide a true and comprehensive description and medical confirmation of the SAE or pregnancy or lactation exposure as it is understood at the time of follow-up. If available, follow-up information should include a summary of the relevant critical data found in medical records (e.g., discharge summaries, lot numbers, relevant laboratory and scan data, and autopsy reports as applicable).

Sponsor will be responsible for obtaining follow-up information for the SAEs occurring in this study (including attempts to obtain medical confirmation) and will demonstrate diligence in attempting to obtain such information by, among other things, maintaining written records of such attempts.

Sponsor will forward all follow-up information to Amgen within the same timeframes that it is required to provide initial reports. The notification of subsequent follow-up information on the same case should reflect the same Sponsor's unique case number.

MedWatch (or equivalent) forms will be used to communicate ICSRs.

All transfer of safety information to Amgen will be made through the designated contact fax or email address listed below:

Fax: 888-814-8653 (toll-free, US)
805-480-9205 (toll)

E-mail: svc-ags-in-us@amgen.com

12.3.1.3.1 Individual Case Safety Report (ICSR)

An ICSR includes Pregnancy Exposure Reports and Follow-up Reports (as those phrases are defined below). Each ICSR shall contain, at a minimum, the following information:

- Event reference number;
- Protocol name and number;
- Sponsor-Investigator contact information;
- Specific subject identifiers (e.g., initials, subject number, date of birth or age, or gender);
- The name of the suspect study drug;
- The date(s) and dosage(s) of exposure;
- Event;
- Date(s) of event;
- Country of event;
- "Serious" Criteria;
- Relationship/causality of study drug;
- Hospitalization history for the event;
- Event status/outcome;
- Relevant history (including diagnostics, laboratory values, radiographs, concomitant medications, and event treatment); and
- Narrative summary.

Every ninety (90) calendar days, ICSRs of all new and follow-up SAEs including Pregnancy Exposure Reports during the preceding 90-day period will be reported on a MedWatch form (or equivalent). Seriousness and causality assessments should be specified. For the avoidance of doubt, the reporting periods begins on the date the first subject enrolls in the study.

12.3.1.4 Reporting to Celgene

Safety events will be reported to Celgene by the Sponsor-Investigator or designee per the timeframes listed below:

Safety Event	Timeframe for Reporting
SUSARs	Within 24 hours of submitting the report to the applicable regulatory authority
SADRs	Within 15 days of Sponsor-Investigator awareness
All other SAEs not meeting definition of SUSAR or SADR (initial and follow-up reports)	Every 90 calendar days, reporting period to begin with date of first subject enrollment.
Special Reporting Situations for lenalidomide	Within 24 hours of Sponsor-Investigator awareness

Any correspondence to the FDA or other Regulatory Authority regarding Adverse Events or other safety issues will be simultaneously copied via facsimile to Celgene. The MedWatch 3500A form should be utilized to report Serious Adverse Events to Celgene, the FDA or other Regulatory Authority (The MedWatch 3500A form will be faxed with the Celgene reference number on the fax cover).

The reporting periods will commence as the date the first subject enrolls in the study. The reporting period ends thirty (30) days after discontinuation of dosing. In addition, any Serious Adverse Event that may occur after this time period which is believed to be certainly, probably or possibly related to the study drug must be reported to Celgene.

12.3.1.4.1 Pregnancy

If a subject becomes pregnant while still being treated with the study drug the Sponsor-Investigator will:

- immediately discontinue at least the treatment with the Celgene study drug;
- instruct the subject to return immediately any unused portion of the Celgene study drug; and
- immediately refer the subject to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Sponsor-Investigator will use reasonable efforts in order to ensure that:

- any study-related pregnant person is advised to consult her general practitioner or gynecologist as soon as possible; and
- the contact details of the healthcare provider who is following the pregnancy are provided to the Sponsor-Investigator.

The Sponsor-Investigator or designee will follow pregnant subjects until the end of the pregnancy and must notify Celgene's Drug Safety Department at fax # 908-673-9115 about the outcome of the pregnancy (including false-positive pregnancy tests) immediately upon having knowledge of the event using the Celgene "Pregnancy Reporting Form" and the Celgene "Follow Up Pregnancy Reporting Form".

The Sponsor-Investigator or designee will report:

- any outcome of a pregnancy which qualifies as a Serious Adverse Event (including spontaneous or therapeutic abortion, fetal and neonatal death or congenital anomaly); and
- any death of an infant which occurs in connection with in utero exposure to the Study Drug within twenty-eight (28) days of birth. The Sponsor-Investigator or designee will also document any congenital anomaly detected in an aborted fetus.
- The Sponsor-Investigator or designee will notify Celgene of any discontinuation of any subject for the reasons set forth in this section using a MedWatch 3500A form.

The Sponsor-Investigator or designee will use their best efforts in order to require that male subjects inform it/him/her if their partners get pregnant while the subject is still treated with the Study Drug and to provide the Sponsor-Investigator or designee the contact details of the healthcare provider who follows the pregnancy in question. Informed consent of the pregnant partner will be required prior to reporting health information on a pregnant partner. Any information provided by the pregnant partner or medical professional following the pregnancy should be reported to Celgene's Drug Safety Department using the Celgene Pregnancy Reporting Form.

12.3.1.4.2 SPM Reporting

Secondary primary malignancy (SPM) is any malignancy which (i) is diagnosed in a study subject in the course of the study or during long-term follow-up, (ii) is different from the malignancy for which the study subject is treated in the context of the study (IPM – initial primary malignancy) and (iii) does not result from metastasis from the IPM. All SPM for the earlier of (x) the period for which the Sponsor and/or Sponsor-Investigator follows the study subjects for survival or (y) for three (3) years following the discontinuation of the study drug will be collected and reported. Such reporting will occur on a quarterly basis via facsimile to Celgene at fax # 908-673-9115 with the Celgene reference number on the fax cover.

12.3.1.5 Reporting to the IRB

All events occurring during the conduct of the protocol and meeting the definition of an SAE will be reported to the IRB per IRB reporting requirements.

12.3.1.6 Reporting to the FDA

According to CFR 312.32, **unexpected fatal or life-threatening events** possibly related with the use of the study drug (drugs) will be reported to the FDA by fax or by email as soon as possible, but in no event later than 7 calendar days after the initial receipt of the information regarding the event. A comprehensive written report will be submitted as an amendment to the IND within an additional 8 days (15 calendar days total).

All other serious unexpected events related to use of the study drug (i.e., serious SARs) will be reported to FDA as an amendment to the IND as soon as possible, but in no event later than 15 calendar days after initial receipt of the information regarding the event.

12.3.2 Reporting UAPs

All UAPs occurring during the conduct of a protocol and meeting the definition of an UAP will be reported to the IRB per IRB reporting requirements.

13. DISEASE EVALUATION

13.1 IMWG 2016 Response Criteria

Please refer to footnotes * and ||. All response categories require two consecutive assessments, which should be captured in the dataset. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

IMWG MRD Criteria (Requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶
Standard IMWG Response Criteria‖; NOTE: see [1] for additional details	
Stringent Complete Response (sCR)	• Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete Response (CR)	• Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates

Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial Response (PR)	• ≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; • If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal Response (MR)	• ≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required.
Stable Disease (SD)	• Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates • Not meeting criteria for CR, VGPR, PR, MR or progressive disease
Progressive disease (PD)¶¶, ||||	Increase of ≥ 25% from lowest response value in any one or more of the following: • Serum M-protein (absolute increase must be ≥0.5 g/dL); • Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; • Urine M-protein (absolute increase must be ≥200 mg/24 h); • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); • Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; • ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical Relapse	Clinical relapse requires one or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of TTP or PFS but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§of the measurable lesion; • Hypercalcaemia (>11 mg/dL);

	• Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein

For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid haemodilution. IMWG=International Myeloma Working Group. MRD=minimal residual disease. NGF=next-generation flow. NGS=next-generation sequencing. FLC=freelight chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features=calcium elevation, renal failure, anaemia, lytic bone lesions. FCM=flow cytometry. SUV_{max}=maximum standardised uptake value. MFC=multiparameter flow cytometry. ^{18}F-FDG PET=^{18}F-fluorodeoxyglucose PET. ASCT=autologous stem cell transplantation.

* All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported. †Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

‡ Bone marrow MFC should follow NGF guidelines.[30] The reference NGF method is an eight-colour two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-colour technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-colour method is most efficient using a lyophilised mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

§ DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta).

¶ Criteria used by Zamagni and colleagues,[85] and expert panel (IMPetUs; Italian Myeloma criteria for PET Use).[81,97] Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUV_{max}=2.5 within osteolytic CT areas >1 cm in size, or SUV_{max}=1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

|| Derived from international uniform response criteria for multiple myeloma.[11] Minor response definition and clarifications derived from Raj Kumar and colleagues.[14] When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the

complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

** All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).
†† Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

‡‡ Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

§§ Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

¶¶ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

|||| In the case where a value is felt to be a spurious result per physician discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.

14. STATISTICAL CONSIDERATIONS

14.1 Milestones

14.1.1 Registration Date

The date the subject signs the informed consent.

14.1.2 Enrollment Date

The date of initiation of study treatment on Cycle 1, Day 1.

14.1.3 Treatment Discontinuation Date

The date the investigator makes the decision to permanently discontinue all protocol directed study treatment. See Section 9 for criteria for discontinuation of treatment.

14.2 Sample Size Determination

The primary objective is to evaluate the efficacy of daratumumab when combined with KRd, in terms of complete response or better, in subjects with newly diagnosed multiple myeloma, and compare to relevant historical controls. For the newly diagnosed multiple myeloma patient population, 8 cycles of KRd induction provides a complete response or better rate of approximately 50% [8,10]. For this population of patients treated with KRd+daratumumab, the aim is to achieve a rate of CR or better of 70%. A minimax 2-stage design will be used to test the hypothesis that the CR or better rate is less than or equal to 50%. Twenty-three (23) evaluable subjects will be enrolled in the first stage, and if at least 12 of the 23 subjects have a complete response or better after induction therapy, an additional 16 evaluable subjects will be enrolled (a total of 39 subjects). If at least 24 of 39 subjects have a complete response or better, the null hypothesis will be rejected. Based on a one-sided alpha = 0.10 significance level, this sample size will provide 90% power to reject the null hypothesis, assuming the true complete response or better rate is 70%.

14.3 Endpoint Definitions

14.3.1 Complete Response or Better

Complete response or better will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of CR or sCR, as determined by the IMWG 2016 response criteria (see Section 13.1).

14.3.2 Overall Response

Objective response will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of PR or better.

14.3.3 Overall Survival (OS)

OS is defined as the duration from enrollment to the study (treatment start date) to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

14.3.4 Progression Free Survival (PFS)

PFS is defined as the duration of time from enrollment to the study (treatment start date) to first occurrence of either progressive disease or death (from any cause), whichever comes first. Disease progression must be objectively determined per IMWG 2016 criteria (see Section 13.1), where the date of progression is the date of the last assessment that identified progressive disease. If the subject died without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not have documented disease progression, PFS will be censored at the date of last disease assessment. For subjects who receive subsequent anti-cancer treatment prior to documented disease progression, PFS will be censored at the date of last disease assessment prior to the commencement of subsequent treatment. Subjects who have an initial PFS event immediately following 2 or more consecutive missed disease

assessments will be censored at the date of the last assessment prior to those missed assessments. For participants with only one missed assessment, the documented progressive disease status and assessment date will be used.

14.3.5 Time to Disease Progression

Time to disease progression (TTP) will be calculated in the same fashion as described for PFS with the exception that for subjects who die for causes other than disease progression, TTP will be censored at the date of the other cause mortality. Otherwise, the censoring mechanism for TTP will be the same as previously described for PFS.

14.3.6 Duration of Response (DoR)

Duration of response (DoR) will be calculated for each subject achieving a PR or better and will be calculated from the time of the first assessment that identified response until disease progression or death. The censoring mechanism for DoR will be the same as described for PFS.

14.3.7 Time to Next Treatment

Time to next treatment (TTNT) will be calculated from the time of treatment start until the start of the first subsequent anti-cancer treatment after all protocol directed therapy is completed. For surviving subjects who do not receive subsequent treatment, TTNT will be censored at the last contact date. For subjects who die before beginning subsequent anti-cancer treatment, TTNT will be censored at the date of death.

14.3.8 Minimal Residual Disease (MRD)

MRD will be determined for each subject at baseline and for each subject with a post-induction VGPR or better after post induction therapy and at subsequent time points as described in the study calendar (Section 7). The MRD assessment will be determined via flow cytometry and DNA sequencing and will be coded as either MRD (+) or MRD (-). Subjects who experience less than a VGPR will be considered to have MRD (+) disease. If a subject does not have an NGS test report available (for whatever reason), the subject will be assumed to be MRD + and will be treated as such per the algorithm. Note: The 10^{-5} MRD result from the NGS MRD test will be used for treatment decisions.

14.3.9 PET/CT Endpoints

For each subject at each time point, number of lesions identified by PET/CT and SUV max will be captured.

14.3.10 Stem Cell Mobilization Endpoints

For each subject, stem cell yield, number of stem cell mobilization attempts, and number of collection days will be captured.

14.3.11 Safety Endpoints

Safety endpoints will include treatment administration (dose intensity, planned dose intensity, and relative dose intensity), AEs, SAEs, deaths while on study treatment.

"Events of Special Interest" (ESI) for Safety Stopping Rule #1

Events of Special Interest (ESIs) will be continuously monitored during the induction phase of the study in subjects receiving the combination of daratumumab, carfilzomib, lenalidomide, and dexamethasone (KRdD) for the purposes of the pre-specified stopping rule described in Section 14.5.6. A binary variable will be determined for each subject indicating whether or not the subject experienced at least one Grade 3/4/5 adverse event related to the KRdD regimen for the following CTCAE terms:

- Heart failure
- Pneumonia
- Dyspnea
- Peripheral edema
- Hypertension

"Events of Special Interest"(ESI) for Safety Stopping Rule #2

A second and separate Events of Special Interest (ESI)will be continuously monitored during the induction phase of the study in subjects receiving the combination of KRdD. The stopping rule for ESI#2 is described in Section 14.5.6. A binary variable will be determined for each subject indicating whether or not the subject died due to an adverse event. The Grade 5 AEs included for this stopping rule will be any hematologic or non-hematologic adverse event, regardless of causality.

14.4 Analysis Populations

The evaluable population consists of the population of subjects who initiate study treatment and who have measurable disease at the baseline disease assessment. Baseline disease assessments are defined as disease assessments collected within 28 days of initiation of the first pre-study induction cycle (subjects who received prior therapy) or within 28 days prior to day 1 of study treatment (subjects with no prior therapy). Enrollment will continue (in both Stage 1 and Stage 2) until the targeted sample sizes are achieved in the evaluable population. Complete and overall response will be analyzed based on the evaluable population. Analyses of other efficacy and safety endpoints will be conducted on the population of subjects who initiate study treatment. Stem cell mobilization endpoints will be evaluated in all subjects who undergo attempt(s) at stem cell mobilization in preparation for ASCT. Exploratory analyses will be conducted on the population of patients who initiate study treatment and who have available biomarker data.

14.5 Analysis Methods

14.5.1 Timing of Analysis

The primary analysis will occur after the best overall response to induction therapy has been determined for all Stage 1 and Stage 2 subjects. Additional analyses are planned at 1 and 3 years after the primary analysis. A final analysis will be conducted after the PFS censoring rate reaches 20% or after all surviving subjects have been on study for at least 5 years, whichever occurs first.

14.5.2 Subject Disposition

An accounting of all consenting subjects will be provided at the end of the study. This will include a breakdown of subjects who consented, were treated, permanently discontinued treatment, died, and were lost to follow-up or withdrew consent.

14.5.3 Baseline Subject and Disease Characteristics

A summary of subject demographics and disease-related characteristics will be completed and subject medical history will be assessed.

14.5.4 Primary Analysis

The frequency and proportion of subjects experiencing a CR or better will be calculated. A corresponding 95% confidence interval will be estimated using the Clopper-Pearson method. A one-sided test for binomial proportions using the rejection regions described in the sample size section (see Section 14.2) will be carried out, testing the null hypothesis that the CR or better rate is less than or equal to 50%.

14.5.5 Secondary Analysis

The frequency and proportion of overall response will be calculated. Corresponding 95% confidence intervals will be estimated using the Clopper-Pearson method. OS, PFS, TTP, DoR, and TTNT endpoints will be analyzed using Kaplan Meier techniques. Selected landmarks will be estimated and reported. Logistic regression models and Cox proportional hazards models will be used to analyze the treatment response endpoints, complete response, overall response, OS, PFS, TTP, and DoR to correlate outcomes to baseline subject and disease characteristics, and results from biomarker studies as previously described. This will include univariate and multivariable regression model techniques to identify individual and independent prognostic factors.

14.5.6 Safety Analysis

The number of study treatment cycles administered, dose intensity, and relative dose intensity will be summarized quantitatively.
Incident rates for TEAEs, AEs leading to study drug discontinuation, SAEs and deaths while on study therapy will be summarized. TEAEs are defined as follows:

- An AE that occurs after treatment start that was not present at the time of treatment start; **OR**
- An AE that increases in severity after treatment start if the event was present at the time of treatment start.

Induction Phase Stopping Rule #1

It is estimated that the composite rate of Grade 3/4/5 ESIs (as defined in Section 14.3.10) in newly diagnosed multiple myeloma patients treated with carfilzomib, lenalidomide, and dexamethasone is approximately 0.40. If it becomes evident that the Grade 3/4/5 ESI rate convincingly exceeds 0.40, then enrollment to the study will be suspended. The decision to suspend enrollment will occur if the posterior probability of the Grade 3/4/5 ESI rate exceeding 0.40 is 0.75 or higher. The prior distribution for this monitoring rule is beta (8,12). This means

that our prior assumptions regarding the Grade 3/4/5 ESI rate are 1) the mean of the prior distribution is 0.40, and 2) there is a 90% probability that this rate is between 0.230 and 0.582. The operating characteristics of the stopping rule are given in the following table and are based on 5000 simulations.

Operating Characteristics of the Stopping Rule #1

Number of Subjects with an ESI #1	Number of Treated Subjects	Posterior Probability: Pr(ESI #1 Rate>0.40|Data)
3	3	0.779
4	5	0.795
5	8	0.755
6	10	0.774
7	12	0.771
8	14	0.793
9	17	0.759
10	19	0.774
11	21	0.788
12	24	0.759
13	26	0.778
14	28	0.788
15	31	0.755
16	33	0.772
17	35	0.806
18	38	0.767

Induction Phase Stopping Rule #2

The stopping rule for the Grade 5 ESI was calculated in a similar fashion as described above. We pooled ESI results from two daratumumab containing regimens [35,36] and estimated the Grade 5 ESI rate to be approximately 0.05. If it becomes evident that the Grade 5 ESI rate convincingly exceeds 0.05, then enrollment to the study will be suspended. The decision to suspend enrollment will occur if the posterior probability of the Grade 5 ESI rate exceeding 0.05 is 0.75 or higher. The prior distribution for this monitoring rule is beta (1,19). This means that our prior assumptions regarding the Grade 5 ESI rate are 1) the mean of the prior distribution is 0.05, and 2) there is a 90% probability that this rate is between 0.002 and 0.146. The stopping rule boundaries are given in the following table. Specifically, the study will be halted if a second death due to an ESI occurs among the first 15 enrolled subjects in the safety population. Otherwise, the study will be halted if a third death due to an ESI occurs among the first 31 subjects enrolled in the safety population. Otherwise, the study will be halted if a fourth death occurs among the first 39 subjects enrolled in the safety population.

Operating Characteristics of the Stopping Rule #2

Number of Subjects with an ESI #2	Number of Treated Subjects	Posterior Probability: Pr(ESI #2 Rate>0.05|Data)
2	15	0.759
3	31	0.760
4	39	0.836

14.5.7 Interim Analysis

A Stage 1 analysis will be conducted after the best overall response has been determined on the first 23 subjects have been enrolled in the evaluable population. Results of the Stage 1 analysis will inform the decision to terminate the study due to futility or continue enrollment to Stage 2.

14.5.8 Exploratory Analysis

The frequency and proportion of subjects achieving MRD (-) evaluated via post-induction DNA sequencing will be summarized, along with a 95% Clopper-Pearson confidence interval. Logistic regression models and Cox proportional hazards models will be used to analyze correlation between systemic immune profiling and clinical response (including outcomes such as MRD [via DNA sequencing], ORR, PFS, and OS). Similar models will be used to assess correlation between circulating T-cell receptor parameters and clinical response. MRD results via flow cytometry and DNA sequencing will be compared using concordance analysis using two by two contingency tables. The MRD agreement rates between the two methods will be estimated. PET/CT response will be determined as a binary variable indicating disappearance of all lesions identified by PET/CT. Correlation between PET/CT response and standard IMWG response will be assessed using Fisher's exact test. The same method will be used to analyze correlation between MRD results (via DNA sequencing) and PET/CT response. Differentially expressed genes between MRD (+) and MRD (-) subjects (via DNA sequencing) will be identified using global gene expression profiling data.

Kaplan-Meier techniques and Cox proportional hazards models will be used to evaluate duration of response, OS, PFS, time to disease progression, and time to next treatment as a function of post-induction MRD status (MRD(-) vs MRD(+)). Logistic regression models will be used to evaluate selected TEAEs as a function of post-induction MRD status.

15. STUDY COMPLETION OR TERMINATION

15.1 Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have died and/or are withdrawn from the study
- All subjects have discontinued from the study
- The IRB, FDA, LCI DSMC, or Sponsor-Investigator discontinues the study because of safety considerations
- The Sponsor-Investigator defines an administrative or clinical cut-off date

15.2 Termination

The study will be terminated when one or more of the following conditions occur:

- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (e.g. SAEs)
    - Results of any interim analysis
    - Results of parallel clinical studies
    - Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
    - If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.
- The Sponsor-Investigator has decided to close the trial at any site and at any time

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow- up, must be taken care of in an ethical manner.

16. STUDY MANAGEMENT

16.1 IRB Approval

The final study protocol and the final version of the informed consent form(s) must be approved in writing by the Sponsor IRB.

The Sponsor-Investigator is responsible for informing the Sponsor IRB of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB annually, as local regulations require.

16.2 Informed Consent

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Written informed consent may include electronic signatures when use of electronic informed consent is obtained from the subject on site or remotely.

16.3 Protocol Adherence

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

16.4 Changes to the Protocol and/or Informed Consent

16.4.1 Amendments to the Protocol

If it is necessary for the study protocol to be amended and/or the informed consent revised, the amendment or a new version of the study protocol (amended protocol) and/or the revised informed consent must be approved by the Sponsor-Investigator, funding company(ies) (if required by the contract(s), the FDA (as applicable) and the Sponsor IRB.

16.4.2 Emergency Modification

The Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the protocol must be explained and documented by the investigator.

16.5 Other Protocol Deviations

If a deviation occurs, the event should be reported to the Sponsor-Investigator promptly. Any IRB reportable event that occurs must be reported to the IRB per IRB requirements.

Protocol deviations that, in the Investigator's judgment, potentially caused harm to participants or others or indicates that the participants or others are at an increased risk of harm, or has adversely impacted data integrity will be reported promptly to the IRB per IRB reporting requirements.

All planned (intentional) protocol deviations must be submitted to the Sponsor-Investigator for approval prior to implementation or planned occurrence. After Sponsor approval has been obtained, planned deviations must be submitted and approved by the IRB prior to the anticipated deviation occurring. Exceptions for eligibility criteria are not allowed.

Planned protocol deviations will be submitted to the FDA and IRB, respectively, for prior approval only if the deviation affects the scientific validity of the study and/or the rights, safety, or welfare of subjects.

16.6 Retention of Records

Essential documentation (e.g. source documents, AEs, records of study drug receipt and dispensation, Sponsor-Investigator correspondence, monitoring reports, and regulatory documents), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

16.7 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by GCP guidelines. The study will also be carried out in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6 and in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. DSMC, IRB, FDA) will be obtained for all participating centers before the start of the study, according to GCP, local laws, regulations and organizations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigators may not modify or alter the procedures described in this protocol. The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Title 21 of the CFR and/or the Declaration of Helsinki. The Sponsor-Investigator is responsible for overseeing the treatment of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

16.8 Confidentiality of Records

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

16.9 Compliance with ClinicalTrials.gov

The Sponsor-Investigator is solely responsible for determining whether the trial and its results are subject to the requirements for submission to ClinicalTrials.gov (http://www.clinicaltrials.gov).

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18. APPENDICES

18.1 Appendix A: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Reference: Oken MM, Creech RH, Hormey RH et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.	

18.2 Appendix B: Cockcroft-Gault Equation

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

18.3 Appendix C: NYHA Classification

Class	Description
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.
Excerpt from Oxford Textbook of Medicine. Vol. 2, p.2228. Oxford Press. 1997.	

18.4 Appendix D: 2014 IMWG Diagnostic Criteria for MM

Clonal bone marrow plasma cells* ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically (1 or more of the following):
  - Hypercalcemia: serum calcium >1 mg/dL higher than the ULN or >11 mg/dL
  - Renal insufficiency: CrCl <40 mL/min (measured or estimated via Cockcroft-Gault; see Appendix B, Section 18.2) or serum creatinine >2 mg/dL
  - Anemia: hemoglobin value of >2.0 g/dL below the lower limit of normal, or a hemoglobin value <10.0 g/dL
  - Bone lesions: 1 or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)-CT‡
- Any one or more of the following biomarkers of malignancy
  - Clonal bone marrow plasma cell* ≥60%
  - Involved/uninvolved serum free light chain ratioÅò ≥100
  - >1 focal lesions on MRI studiesÅ˜

*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohisto-chemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.
ÅòThese values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.
Å˜Each focal lesion must be 5 mm or more in size.

See Reference [26] for full details.

18.5 Appendix E: Assessment of Asthma Severity

- **Classifying severity for patients who are not currently taking long-term control medications.**

Components of Severity		Classification of Asthma Severity (Youths ≥12 years of age and adults)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment Normal FEV_1/FVC: 8–19 yr 85% 20–39 yr 80% 40–59 yr 75% 60–80 yr 70%	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1x/day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC normal	• FEV_1 ≥80% predicted • FEV_1/FVC normal	• FEV_1 >60% but <80% predicted • FEV_1/FVC reduced 5%	• FEV_1 <60% predicted • FEV_1/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			

- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

Source: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (nih.gov)[44]
https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf

18.6 Appendix F: Assessment of Asthma Control

FIGURE 3–5c. ASSESSING ASTHMA CONTROL IN YOUTHS ≥12 YEARS OF AGE AND ADULTS

Components of Control		Classification of Asthma Control (Youths ≥12 years of age and adults)		
		Well-Controlled	Not Well-Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakening	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated Questionnaires			
	ATAQ	0	1–2	3–4
	ACQ	≤0.75*	≥1.5	N/A
	ACT	≥20	16–19	≤15
Risk	Exacerbations	0–1/year	≥2/year (see note)	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term followup care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.

Key: EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second. See figure 3–8 for full name and source of ATAQ, ACQ, ACT.

Notes:

- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

Source: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (nih.gov)[44]
https://www.nhlbi.nih.gov/sites/default/files/media/docs/EPR-3_Asthma_Full_Report_2007.pdf