PROTOCOL INFORMATION

Study Title: MONOCLONAL ANTIBODY-BASED SEQUENTIAL THERAPY FOR DEEP REMISSION IN MULTIPLE MYELOMA – MASTER TRIAL

NCT # 03224507
UAB # 1735
Amgen # ISS -20167173
Janssen# 54767414MMY2018
IND#135181

Protocol team:

Yelak Biru (patient advocate)

Natalie S. Callander, MD

Robert Frank Cornell, MD

Luciano J. Costa, MD, PhD (**Chair, sponsor-investigator**)

Saurabh Chhabra, MD

Parameswaran Hari, MD

Eva Medvedova, MD

James Omel, MD (patient advocate)

Sponsor:

University of Alabama at Birmingham

Support:

Amgen (funding and investigational agent)

Janssen (funding and investigational agent)

Statistician:
Name: Yufeng Li
Address: MT 644, 1717 11th Ave S, Birmingham, AL 35294-4410
Phone No: 205.934.3679
Fax No: 205.934.4262
Email Address: yli@uabmc.edu

University of Alabama at Birmingham, Clinical Trials Network and Monitoring Office – UAB CTNMO
(Multicenter Operations)

Name: Pam Dixon Hardwick, RN, OCN, CCRP
Address: 1802 6th Avenue South; NP 2515, Birmingham, AL 35294
Phone: (205) 975-5387
Fax No: (205) 975 9875
Email Address: pamdixon@uab.edu

Protocol Version History:

Original date May 19, 2017
Amendment #1 October 30, 2017
Amendment #2 May 21, 2018
Amendment #3 Feb 14, 2019
Amendment #4 Aug 19, 2019
Amendment#5 Nov 15, 2019
Amendment#6 Feb 12, 2022

PROTOCOL SYNOPSIS

TITLE: MONOCLONAL ANTIBODY-BASED SEQUENTIAL THERAPY FOR DEEP REMISSION IN MULTIPLE MYELOMA – MASTER TRIAL

OBJECTIVES:

PRIMARY OBJECTIVE

To determine the frequency of MRD(-) remissions ($\leq 10^{-5}$ MM-associated molecules) after completion of intense treatment plan that consist of induction therapy, followed by consolidation therapy with a multi-drug regimen combined with continuous daratumumab therapy in patients with newly diagnosed multiple myeloma

SECONDARY OBJECTIVES

To determine the toxicity profile of the combination of carfilzomib, lenalidomide, dexamethasone and daratumumab (KRdD) in the treatment of patients with newly diagnosed MM.

To determine the frequency of Imaging plus MRD-negative patients ($\leq 10^{-5}$ MM-associated molecules in bone marrow and no area of PET/CT FDG uptake greater than mediastinal blood pool or surrounding normal tissue).

To determine the frequency of MRD(-) status after induction therapy with KRdD

To determine the frequency of conversion from MRD(+) to MRD(-) status with auto-HCT after completion of KRdD induction.

To determine the frequency of patients achieving complete remission (CR) with the above mentioned treatment regimen.

To determine the feasibility and effectiveness of MRD-guided treatment discontinuation in newly diagnosed MM patients that have confirmed MRD(-).

To determine the risk and timing of resurgence of MRD ($\geq 10^{-5}$) after discontinuation of therapy in confirmed MRD(-) patients

EXPLORATORY OBJECTIVES

To estimate PFS in cytogenetically defined high-risk patients [myeloma harboring t(4;14), t(14;16), del17p] and cytogenetically defined standard risk patients who discontinue therapy upon confirmed MRD<10^{-5}

STUDY DESIGN: Single arm, multi-center, open label phase 2 trial with safety lead in and response-adapted therapy.

STUDY POPULATION: Adult patients with newly diagnosed multiple myeloma and indication for initiation of therapy

INCLUSION CRITERIA:

1. Age >18 years with no upper age limit
2. Diagnosis of newly diagnosed multiple myeloma with indication for initiation of therapy.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0–2
4. No prior MM-directed therapy except for dexamethasone (up to 160 mg) and/or bortezomib (up to 5.2 mg/m^2) and/or cyclophosphamide up to 1000 mg/m^2 administered for management of acute manifestations of MM (hypercalcemia, renal impairment, pain) for no longer than 4 weeks prior to enrollment (pre induction). If subject received any prior therapy, pretreatment parameters necessary for disease characterization and response assessment must be available.
5. Measurable disease meeting at least one of the following criteria (at screening or prior to pre induction):
   - -Serum monoclonal (M) protein ≥1.0 g/dl
   - -≥ 200 mg of M protein/24h in the urine
   - -Serum free light chain ≥10 mg/dL and abnormal kappa to lambda ratio.
6. Available FISH report (performed locally or by third party cytogenetics laboratory) that informs absence or presence of

high risk chromosome abnormalities [del17p, t(4;14) and t(14;16)]

7. Life expectancy ≥ 12 months.
8. Adequate hepatic function, with serum ALT ≤ 3.5 times the upper limit of normal and serum direct bilirubin ≤ 2 mg/dL (34 µmol/L) within 21 days prior to initiation of therapy.
9. Creatinine clearance (CrCl) ≥ 40 mL/minute within 21 days prior to start of therapy either measured or calculated using standard Cockcroft and Gault formula (available in https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc).Written informed consent in accordance with federal, local, and institutional guidelines.
10. Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception during treatment and for 30 days after the last dose of carfilzomib. Male subjects must agree to practice contraception and refrain from donating sperm during treatment and for 90 days after the last dose of carfilzomib.
11. All subjects must agree to comply with and be enrolled in Revlimid REMS™ program.

EXCLUSION CRITERIA:

1. Diagnosis of amyloidosis, POEMS, Waldenstrom's macroglobulinemia.
2. Major surgery, radiotherapy or infection requiring therapy within 14 days of starting treatment.
3. Known FEV1 or cDLCO < 50% of predicted.
4. Pregnant or lactating females.
5. Known human immunodeficiency virus infection.
6. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker)

AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

7. 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).
8. Unstable angina or myocardial infarction within 4 months prior to registration, NYHA Class II, III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker.
9. Cerebrovascular disease manifested as prior stroke at any time or TIA in the 12 months prior to initiation of therapy
10. Nonhematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or localized thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas.
11. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 21 days prior to registration.
12. Known history of allergy to Captisol® (a cyclodextrin derivative used to solubilize carfilzomib).
13. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 21 days prior to registration.
14. Contra indication or intolerance to required supportive care medications (Aspirin and Acyclovir)
15. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

STUDY PROCEDURES:

Initially 6 patients will be enrolled in a safety lead-in. If dose limiting toxicity is seen during the first 2 cycles in 2 or more subjects, the study will be reviewed by the data safety monitoring

board that may recommend protocol amendment. If less than 2 subjects develop dose-limiting toxicity during the first 2 cycles of therapy accrual will continue at the initial dose level.

With approval of protocol amendment 2 (PA2) and change on dose and schedule of carfilzomib (from 6 to 3 doses per cycle), the next 6 patients starting therapy will be considered to be in a safety lead-in at the new dose and schedule and followed the same procedure outlined above. Once a new dose and schedule is declared safe, previously enrolled patients will switch from 6 doses of carfilzomib to 3 doses of carfilzomib per cycle.

Subjects are expected to transition from induction therapy, to consolidation therapy and from consolidation therapy to observation/ maintenance therapy according to MRD status. Autologous hematopoietic cell transplantation (auto-HCT) is the initial step in consolidation therapy. Subjects not eligible for auto-HCT (per investigator's assessment) or who choose to defer auto-HCT will receive four additional cycles of consolidation therapy as "replacement" for auto-HCT. Each cycle of therapy has duration of 4 weeks, except for auto-HCT that is expected to last 16 weeks (including recovery)

INDUCTION THERAPY

Screening – Subjects likely to meet eligibility criteria will be offered participation in the study after the investigator verifies UAB CTNMO registration. Subjects will sign informed consent prior to any protocol associated procedure. Screening procedures are outlined in Table 7 and will ensure that subject 1) meets all the eligibility criteria, 2) obtain disease assessment to allow efficacy

measurements, 3) assess baseline toxicity, and 4) provide identification samples for subsequent MRD assessment.

KRdD Induction Therapy- The total duration of induction is 4 cycles of 28-day duration each. In all cycles patients will receive dexamethasone 40 mg oral on days 1,8,15 and 22 and lenalidomide 25 mg (see adjustment for renal impairment in Table 5) daily from days 1-21. During cycle 1 of induction therapy, subjects will be treated on a distinct schedule to avoid overlap of toxicities associated with first dose of daratumumab and toxicities associated with first dose of carfilzomib. During cycles 1 and 2 subjects will receive daratumumab 16 mg/kg on days 1,8,15 and 22. During cycles 3 and 4 subjects will receive daratumumab 16 mg/kg on day 1 and 15 of each cycle. Carfilzomib will be administered at dose of 20 mg/m^2 on day 8 of first cycle and at dose of 56 mg/m^2 on days 15 of first cycle and days 1,8,15 of subsequent induction cycles.

Response assessment- Response assessment based on serum and urine protein electrophoresis, serum and urine immunofixation and serum free light chains will occur at the end of cycles 2 and 4 of induction. Bone marrow aspiration with MRD assessment (in subjects found to be MRD-informative based on clone identification sample) will be performed at the end of cycle 4 (hereafter referred to as induction MRD).

CONSOLIDATION THERAPY

Auto-HCT – Upon completion of induction therapy patients will proceed with standard of care auto-HCT (consolidation 1). Hematopoietic progenitor cell mobilization will be performed utilizing growth-factors with or without the addition of plerixafor using standard practices. The use of chemotherapy mobilization is not allowed as it may add toxicity, delay transplant and post-

transplant recovery. Chemotherapy mobilization may be employed after failure of initial mobilization attempt and after discussion with study PI. Subjects who are transplant eligible (as determined by investigator), but choose to defer transplant, will collect hematopoietic progenitor cells and them proceed to KRdD consolidation. Auto-HCT conditioning therapy with consist of Melphalan 200mg/m^2 administered as single dose on day -2 or -1. Supportive care following auto-HCT will follow standard of care institutional practices. Subjects will resume consolidation therapy not earlier than 90 days and ideally not later than 112 days after auto-HCT.

KRdD consolidation therapy- The total duration of KRD consolidation (consolidations 2 and 3) will be up to 8 cycles (up to 12 cycles for patients who don't undergo auto-HCT) of 28-day duration each. In all cycles patients will receive dexamethasone 40 mg oral on days 1,8,15 and 22 and lenalidomide 25 mg (see adjustment for renal impairment in Table 5) daily from days 1-21, daratumumab 16 mg/kg on day 1 and 15 on the first two cycles of consolidation and on day 1 on remaining cycles and carfilzomib 56 mg/m2 on days 1,8,15.

Response assessment- Response assessment based on serum and urine protein electrophoresis, serum and urine immunofixation and serum free light chains will occur 60-80 days after auto-HCT and at the end of each even cycle during KRdD consolidation. Bone marrow aspiration with MRD assay (in subjects found to be MRD-informative based on clone identification sample) will be performed 60-80 days after auto-HCT (or on day 1 of cycle 3 of KRdD consolidation#1 for patients not undergoing auto-HCT), hereafter

referred to as consolidation-1 MRD , and, when applicable, on day 1 of cycles 3 KRdD consolidation (cycle 7 for subjects who did not undergo auto-HCT) hereafter referred to as consolidation-2 MRD and on day 1 of cycle 7 of KRdD consolidation (cycle 11 for subjects who did not undergo auto-HCT) hereafter referred to as consolidation-3 MRD . This approach of assessing MRD at the beginning of the third cycle of each 4-cycle "block" of KRdD allows patients who have become confirmed MRD(-) to effectively receive two full cycles of consolidation (the third and fourth cycle in the block) before having therapy discontinued.

OBSERVATION/MAINTENANCE THERAPY

Transition to observation/maintenance therapy – Subjects will start observation/maintenance therapy after completing the entire planned consolidation therapy or after obtaining a confirmed MRD(-), defined as $\leq 10^{-5}$ MM-associated molecules in 2 consecutive tests, that is induction-MRD plus consolidation-1 MRD or consolidation-1 MRD plus consolidation-2 MRD or consolidation -2 MRD and consolidation-3 MRD.

MRD negative observation cohort– Subjects who obtain confirmed MRD(-) assessment in either consolidation-1 MRD or consolidation-2 MRD or consolidation-3 MRD will be managed in the MRD (-) observation cohort. In this cohort, subjects will be observed without MM-directed therapy and undergo monitoring, including MRD surveillance during an active surveillance phase (72 weeks). Subjects who test positive for MRD at any of the subsequent surveillance MRD assessments while off therapy are encouraged to start standard of care maintenance lenalidomide as discussed for MRD(+) cohort.

MRD negative cohort disease assessment- Response assessment based on serum and urine protein electrophoresis, serum and urine immunofixation and serum free light chains will occur at a minimum of every 8 weeks for the first 24 weeks and every 16 weeks thereafter. Bone marrow aspiration with MRD surveillance will be performed 24 and 72 weeks after start of observation.

MRD positive maintenance cohort– Subjects who are not evaluable for MRD status or don't have confirmed MRD(-) at the end consolidation-3 will not receive more experimental therapy beyond consolidaton-3 and will be observed in the MRD(+) cohort. In this cohort subjects will be monitored for overall and progression-free survival. It is highly recommended that subjects receive standard of care lenalidomide maintenance. Recommended starting regimen is lenalidomide 10 mg/day continuously until progression or intolerance, with dose modifications and adjustments being performed at treating physician discretion.

MRD positive cohort disease assessment- Response assessment based on serum and urine protein electrophoresis, serum and urine immunofixation and serum free light chains is strongly recommended not less often than every 16 weeks until disease progression .

PRIMARY ENDPOINT:	Rate of MRD negative remissions ($\leq 10^{-5}$ MM-associated molecules) at completion of consolidation therapy.
SECONDARY ENDPOINTS:	Toxicity profile of the KRdD combination.

Rate of Imaging plus MRD-negative patients ($\leq 10^{-5}$ MM-associated molecules in bone marrow and no area of PET/CT FDG uptake greater than mediastinal blood pool or surrounding normal tissue)

Rate of negative MRD at completion of induction.

Rate of conversion from positive to negative MRD with auto-HCT.

Rate of achievement of complete remission (CR) upon completion of induction and consolidation.

Rate and kinetics of conversion from negative MRD to positive MRD upon treatment discontinuation.

Progression-free survival (PFS) and overall survival (OS) for entire study population.

EXPLORATORY ENDPOINT:

PFS for patients with confirmed MRD(-) and undergoing observation without additional therapy.

STATISTICAL METHODS:

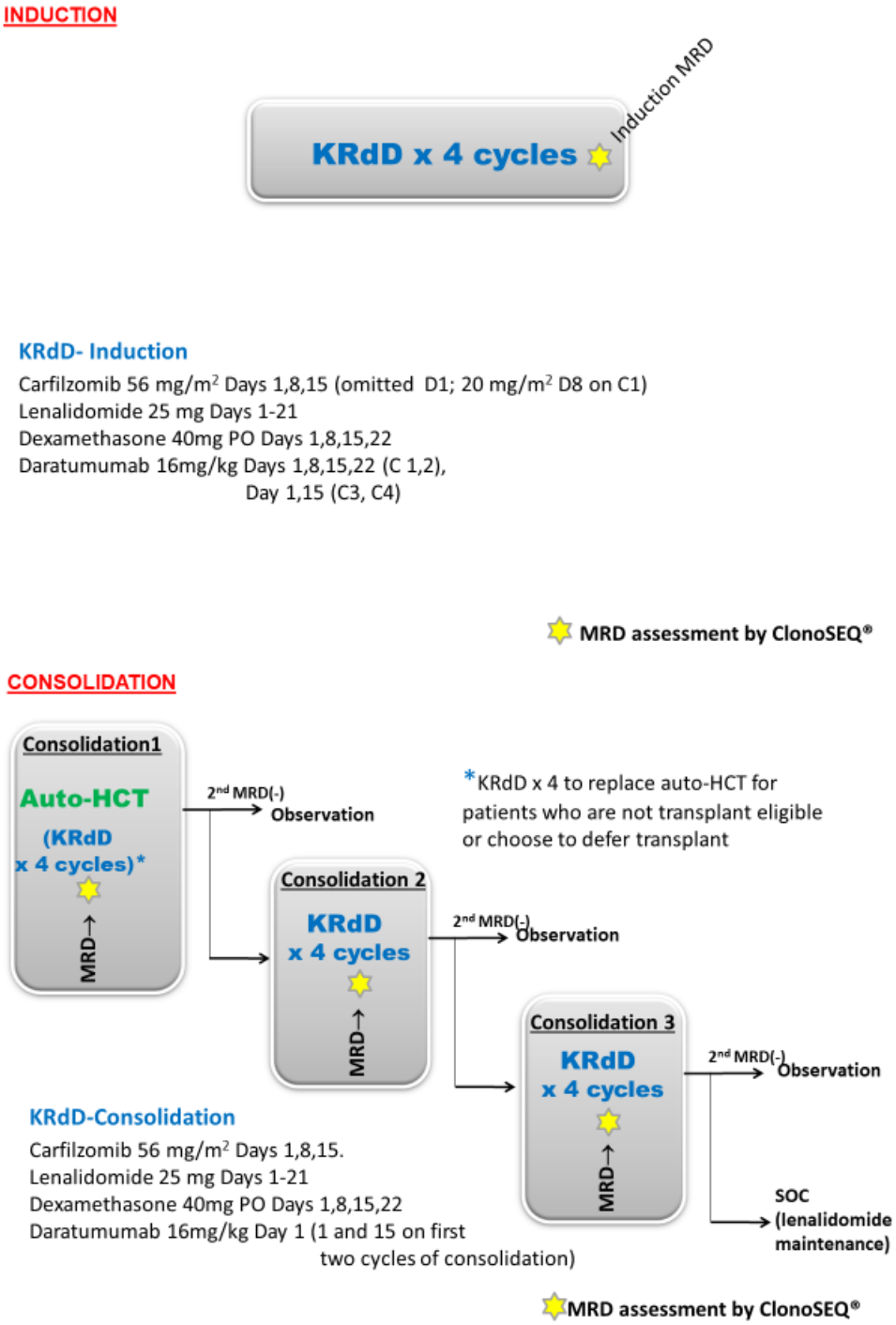
Due to limited data on the safety of the specific combination of agents being studied in the induction phase, a safety lead-in was performed and included 6 subjects. No dose limiting toxicity was seen during the first 2 cycles in 2 or more subjects (in fact, none of the first 6 subjects experienced dose limiting toxicity). The study

was reviewed by the data safety monitoring board that recommended accrual will continue at the initial dose level.

Using Simon's optimal two-stage design (optimal design), a total of 67 evaluable patients will achieve 80% power to detect at least 15% more MRD negative subjects in the experimental intervention compared to the historical benchmark (60% MRD negative rate at a KRd + auto-HCT trial) aiming to achieve at least 75% MRD negative upon completion of consolidation in the current protocol. Twenty seven patients will be enrolled in the first stage; the trial will be terminated if 17 or fewer patients become MRD negative in the first stage. If the trial goes on to the second stage, an additional 40 evaluable patients (total of 67 evaluable patients) will be studied. If the total number of subjects to become MRD negative is less than or equal to 46, the intervention will be considered futile. By accounting for 20% of either subject drop out or not informative for MRD, a total of 82 eligible patients will be required.

Upon approval of protocol amendment 4, as long as protocol has not met criteria for early stop at first stage and does not meet criteria for futility upon completion of second stage, accrual will continue to a total of 123 patients, being 77 standard risk (SR) and 44 high risk (HR) patients. The expansion will enable the exploratory objective to describe PFS on HR and SR patients with confirmed MRD (-) status.

SCHEMA


INDUCTION
KRdD x 4 cycles
Induction MRD
KRdD- Induction
Carfilzomib 56 mg/m2 Days 1,8,15 (omitted D1; 20 mg/m2 D8 on C1)
Lenalidomide 25 mg Days 1-21
Dexamethasone 40mg PO Days 1,8,15,22
Daratumumab 16mg/kg Days 1,8,15,22 (C 1,2),
Day 1,15 (C3, C4)
MRD assessment by ClonoSEQ®
CONSOLIDATION
Consolidation1
Auto-HCT
(KRdD
x 4 cycles)*
MRD
2nd MRD(-)
Observation
*KRdD x 4 to replace auto-HCT for patients who are not transplant eligible or choose to defer transplant
Consolidation 2
KRdD
x 4 cycles
MRD
2nd MRD(-)
Observation
Consolidation 3
KRdD
x 4 cycles
MRD
2nd MRD(-)
Observation
SOC
(lenalidomide
maintenance)
KRdD-Consolidation
Carfilzomib 56 mg/m2 Days 1,8,15.
Lenalidomide 25 mg Days 1-21
Dexamethasone 40mg PO Days 1,8,15,22
Daratumumab 16mg/kg Day 1 (1 and 15 on first
two cycles of consolidation)
MRD assessment by ClonoSEQ®

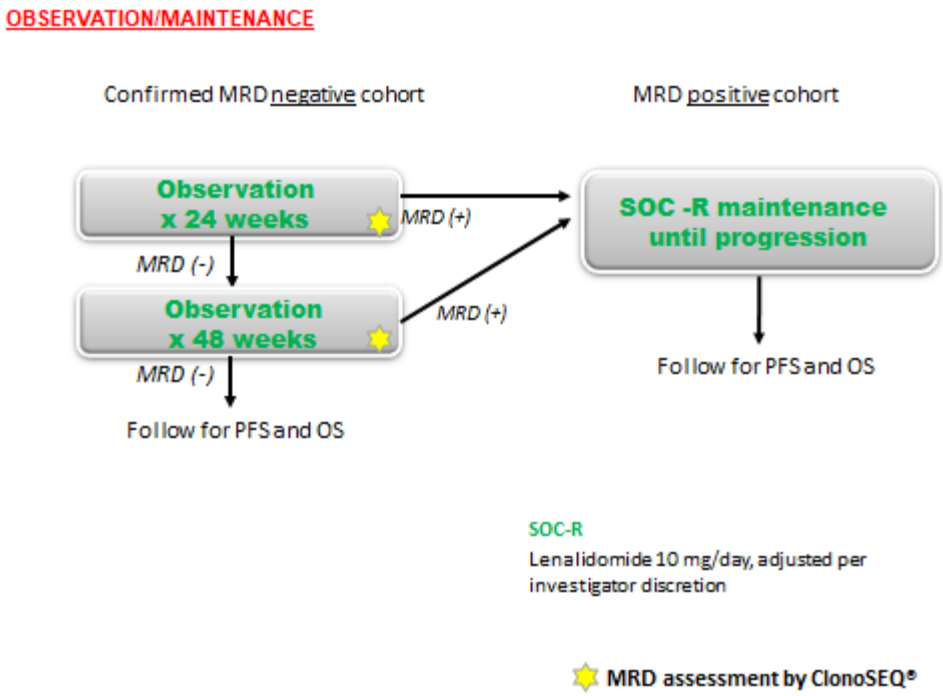

OBSERVATION/MAINTENANCE
Confirmed MRD negative cohort
MRD positive cohort
Observation x 24 weeks
MRD (+)
SOC -R maintenance until progression
MRD (-)
Observation x 48 weeks
MRD (+)
MRD (-)
Follow for PFS and OS
Follow for PFS and OS
SOC-R
Lenalidomide 10 mg/day, adjusted per investigator discretion
MRD assessment by ClonoSEQ®

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
°C	degrees Centigrade
°F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time (also PTT)
AST	aspartate aminotransferase
bid	twice daily
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CR	complete response
CrCl	Creatinine Clearance
CRF	case report form(s)
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
dL	deciliter
DLT	dose-limiting toxicity
DVT	deep venous thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FLC	free light chain
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage colony stimulating factor
h	hour(s)
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	intravenous
kg	kilogram(s)
LDH	lactate dehydrogenase
LTD	last tolerated dose
mg	milligram(s)
min	minute(s)
mIU	Milli International Units
mL	milliliter(s)
MM	multiple myeloma
mm^2	millimeter(s) squared
mm^3	millimeter cubed
MR	minimal response
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (oral)
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QIU	Qualified Investigator Undertaking Form
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SPEP	serum protein electrophoresis
STD_{10}	severely toxic dose in 10% of animals
TLS	Tumor lysis syndrome
TTP	time to tumor progression
ULN	upper limit of the normal range
UPEP	urine protein electrophoresis

VGPR	very good partial response
WBC	white blood count

1 INTRODUCTION

1.1 DISEASE SPECIFIC BACKGROUND

Multiple Myeloma (MM) is a malignant plasma cell disorder with no standard curative therapy(1) . Symptomatic MM is characterized by a clonal proliferation of plasma cells preceding clinical findings that include bone lesions, fractures, anemia, renal failure and hypercalcemia.(2) MM is the second most common hematologic malignancy in the US with 30,330 expected new cases in 2016(3).

For decades, low doses of melphalan and prednisone was the cornerstone of MM treatment. However, complete responses under this regimen are rare, and the median time for progression is not higher than 15 months (4, 5). A first significant advance in the management of MM was the upfront use of high doses of melphalan with autologous hematopoietic cell transplantation (auto-HCT), typically after short induction therapy. Such treatment has allowed for improved response rates, progression free survival and prolonged survival in MM(6-9) and its value has been recently confirmed even in the setting of modern induction therapy(10, 11). High dose melphalan with AHSCT therefore remains a fundamental therapeutic modality as part of the initial therapy for patients with newly diagnosed MM.

Induction therapy for patients with newly diagnosed MM (NDMM) has also evolved substantially. The use of the proteasome inhibitor bortezomib in the setting of 3-drug regimens has produced remission rates in >90% of patients, is well tolerated, and prolongs survival over non-bortezomib containing regimens in patients who proceed to auto-HCT as well as patients who remain on conventional therapy(12, 13).

A major change in paradigm in upfront myeloma therapy has been the transition from fixed duration of therapy to continuous therapy, of ten in the format of single agent maintenance therapy after either conventional induction(14, 15) or induction followed by auto-HCT consolidation(14, 16, 17). This approach has impacted the duration of remission and, in a subset of studies, also overall survival (15, 16).

Despite impressive rates of complete remissions with induction therapy and implementation of maintenance therapy, the vast majority of MM patients will experience a relapse and eventually succumb to the disease, typically after several additional lines of therapy. This observation highlights the discrepancy between obtaining complete response to therapy by

traditional response criteria and obtaining definitive disease eradication as well as the need to develop more active treatment regimens and better tools for response assessment.

1.2 MINIMAL RESIDUAL DISEASE IN MM

More recently, the development and validation of minimal residual disease (MRD) assessment by next generation sequencing (NGS) has allowed identification of group of patients with very distinct prognosis according to the burden of disease despite being all in the same traditional category of hematologic response(18-20).

The DFCI/IFM 2009 trial treated patients with a combination of bortezomib, lenalidomide and dexamethasone (VRD) as induction, followed by randomization between immediate and deferred auto-HCT with subsequent VRD consolidation in both arms and lenalidomide maintenance(11). Patients with pre maintenance MRD(-) had much improved progression free survival (>80% at 2 years) than patients MRD(+), identifying a subset of patients who may be cured from the disease and validating a disease assessment tool that may be employed for response-adapted therapy(18, 21). MRD assessment by NGS is currently available in the US as ClonoSEQ® test.

Other modalities of MRD assessment in MM include flow cytometry and allele-specific polymerase chain reaction. These modalities are currently less attractive as a management tool due to lower sensitivity, limited cross-validation, limited applicability and/or higher cost.

In a recent consensus paper the International Multiple Myeloma Working Group (IMWG) defined MRD negative status as $< 10^{-5}$ cells by flow cytometry or NGS. In this study we intend to also report MRD negative rates according to IMWG definition, however for MRD-adapted therapy we will utilize the more conservative approach of requiring confirmed (2 consecutive tests) MRD negativity ($\leq 10^{-5}$) to drive abbreviation and discontinuation of therapy.

Functional imaging as FDG-PET scan can add to bone marrow-based MRD testing by indicating residual foci of myeloma in bone and soft tissue and has been correlated with prognosis(22).

While initial series using higher threshold for MRD detection indicated that MRD and cytogenetic abnormalities both contribute to post-remission prognosis(23, 24), more recent series

using more sensitive MRD assays indicate that elimination of MRD may trump even the initial cytogenetic risk classification(21, 25).

1.3 CARFILZOMIB BACKGROUND

The proteasome is a multicatalytic proteinase complex that is responsible for degradation of a wide variety of protein substrates within normal and transformed cells. Intracellular proteins targeted for degradation by the proteasome are first ubiquitinated via the ubiquitin conjugation system. Ubiquitinated proteins are cleaved within the proteasome by one or more of three separate threonine protease activities: a chymotrypsin-like activity, a trypsin-like activity, and a caspase-like activity.

Carfilzomib (PR-171, Kyprolis®) is a tetrapeptide ketoepoxide-based inhibitor specific for the chymotrypsin-like active site of the 20S proteasome. Carfilzomib is structurally and mechanistically distinct from the dipeptide boronic acid proteasome inhibitor bortezomib (Velcade®). 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(26, 27).

Carfilzomib was initially approved in the US after demonstrating single agent activity in patients with relapsed and refractory multiple myeloma(28, 29), initially at the dose of 27 mg/m^2 on days 1,2,8,9, 15 and 16 of each 28-days cycle, with the dose being reduced to 20 mg/m^2 on the first cycle.

Subsequently, the dose of carfilzomib has been escalated in an attempt to improve anti-myeloma activity. In a phase 1 study, the maximal tolerated dose of single agent carfilzomib was found to be 56 mg/m^2 utilizing the traditional schedule and longer infusion time (30 minutes)(30). This regimen led to 55% overall response rate in an independent phase 2 trial of heavily pretreated patients (31). The toxicity profile of higher dose of carfilzomib was not clearly distinct from the initial dosing with the most common grades 3 or 4 adverse events (AEs) being lymphopenia, thrombocytopenia, hypertension, pneumonia and heart failure.

The Endeavor trial was the first to directly compare two proteasome inhibitors, namely bortezomib and carfilzomib, in patients with relapsed MM and 1-3 prior lines of therapy(32). Bortezomib was administered by subcutaneous (79%) or intravenous (21%) routes and conventional schedule and doses in combination with dexamethasone (Vd). Carfilzomib was administered at conventional schedule but in higher doses, 20 mg/m2 on days 1 and 2 of first cycle and 56 mg/m2 thereafter also in combination with dexamethasone (Kd). Kd led to higher rate of response and median improvement in PFS by 9.3 months. Patients treated with Kd were more likely to develop grade 3 or higher heart failure (5% vs. 2%) but less likely to develop grade 3 or higher peripheral neuropathy (2% vs. 8%) than patients treated with Vd.

Investigators have also explored the use of higher doses of carfilzomib on a less intense schedule, allowing for greater convenience. The Champion 1 study explored weekly carfilzomib (i.e. days 1,8,15 of each 28 day cycle) as single agent and found the dose of 70 mg/m^2 to be the maximum tolerated, leading to objective responses in 77% of patients with relapsed and refractory MM(33). More recently, the ARROW study compared weekly carfilzomib at 70 mg/m^2 with the traditional schedule at 27 mg/m^2 in patients with relapsed and refractory MM and found the weekly dose to have similar safety profile and more prolonged progression-free survival(34).

1.3.1 CARFILZOMIB COMBINATION WITH LENALIDOMIDE AND DEXAMETHASONE

Prior phase 1 and 2 studies demonstrated the safety and efficacy of the combination of lenalidomide (revlimid®), dexamethasone and carfilzomib in treating patients with relapsed myeloma(35). Aspire was a large international phase 3 trial comparing this triple combination (KRd) vs. lenalidomide plus dexamethasone (Rd) in patients with relapsed or refractory MM and 1-3 prior lines of therapy(36). Carfilzomib was administered on days 1, 2, 8, 9, 15 and 16 of each 28-days cycle at 20 mg/m^2 on days 1 and 2 of first cycle and 27 mg/m^2 thereafter, reduced to days 1,2,15 and 16 after cycle 12 and discontinued after cycle 18. KRd was superior to Rd in progression-free survival (primary endpoint), overall response rate and, importantly, also quality of life. Patients randomized to KRd were more likely to develop hypertension (grade 3 or higher 4.3% vs. 1.8%) and congestive heart failure (grade 3 or higher 3.8 vs 1.8%).

The KRd combinations has also been tested in the treatment of patients with newly diagnosed MM producing 61% of stringent CR and 24-month PFS rate of 92% in one study(37). In another study including a subset of patients with smoldering MM, the combination of carfilzomib, lenalidomide and dexamethasone led to 100% of VGPR or better. Importantly, among the 67% of patients who achieved MRD negative status by NGS, none progressed in the first 12 months of therapy (19).

1.4 DARATUMUMAB BACKGROUND

Daratumumab is a human IgG1 kappa monoclonal antibody directed at CD38, a transmembrane protein that is overly expressed on plasma cells and malignant myeloma cells, while having low expression on normal lymphoid, myeloid, as well as epithelial tissue.(38) Functionally, daratumumab directly targets CD38-expressing tumor cells and promotes antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity and apoptosis.(39) Preclinical data has demonstrated robust antitumor activity in xenograft models, including those with lenalidomide and bortezomib resistant cell lines.(39) Daratumumab (Darzalex®) is approved for treatment of relapsed MM, or newly diagnosed transplant ineligible MM, in combination with bortezomib, melphalan and prednisone.

DARATUMUMAB SINGLE AGENT

The phase 1/2 GEN501 study of daratumumab monotherapy enrolled consecutive cohorts receiving daratumumab from 0.005 to 24 mg/kg/dose(40) and identified 16mg/kg as the ideal dose with main toxicity being infusion-related events (IREs), mostly pyrexia, cough, dizziness, and bronchospasm. Efficacy was reported for the doses of 8mg/kg and 16 mg/kg and patients receiving the 16mg/kg dose had improved ORR (36%) and PFS (5.6 months) compared with the 8mg/kg.

The MMY2002 “Sirius” study randomized patients with 3 or more prior lines of therapy including a PI and an IMiD or double refractory to PI and IMiD to be treated with single agent

daratumumab at either 8mg/kg or 16 mg/kg every week for 8 weeks, then every other week for 16 weeks and every week afterwards. Overall 106 patients were accrued to the 16 mg/kg arm. IREs were seen in 42% of patients, mostly during first infusion. In the 16 mg/kg arm the overall response rate was 29.2% and median duration of response was 7.4 months(41).

1.4.2 DARATUMUMAB COMBINATIONS

In the phase 1/2 GEN 503 study, patients with relapsed MM received daratumumab in combination with lenalidomide and dexamethasone. Among the 32 patients who received daratumumab at 16mg/kg, the ORR was 88%, with 53% reaching VGPR or better. Grade 3 or 4 neutropenia was seen in 75% of subjects, but febrile neutropenia was uncommon. IREs occurred in 56% of patients with only 6% being grade 3(38).

The synergistic effect of daratumumab and IMiDs was further demonstrated with the combination of daratumumab, pomalidomide and dexamethasone in 77 patients with at least 2 prior lines of therapy including prior treatment with lenalidomide and bortezomib. IREs occurred at a rate (61%) similar to daratumumab single agent or in combination with lenalidomide and dexamethasone. Neutropenia was the most common grade 3 or higher toxicity (55%). Objective responses were seen in 59% of patients, including 58% of the double refractory patients (42).

Two randomized phase 3 trial have further solidified the benefit of daratumumab combinations with IMIDs or with PI. In the CASTOR trial patients with relapsed and refractory MM were randomized to receive bortezomib and dexamethasone with or without the addition of daratumumab. The rate of VGPR or better was higher in the daratumumab arm (59.2% vs. 29.1%, P<0.001) as was median progression-free survival (not reached vs. 7.2 months, HR 0.39, P<0.001(43). Using an IMID backbone, The POLLUX trial randomized patients with relapsed MM and at least one prior line of therapy to receive lenalidomide plus dexamethasone with or without daratumumab. The rate of VGPR or better was higher in the daratumumab arm (75.8% vs. 44.2%) and media progression-free survival was not reached for the daratumumab arm vs. 18.4 months in the control group (HR 0.37, P<0.001)(44)

1.5 STUDY RATIONALE

The KRd combination can induce high frequency of deep and durable remissions in patients with MM, particularly when consolidation is provided with auto-HCT. In fact a recent comparison between KRd conventional treatment and KRd followed by auto-HCT indicates further improvement in the depth of remissions with auto-HCT (sCR at 18 months 87% vs. 55%)(45). There is limited overlapping toxicity between daratumumab and any of the agents in KRd. Additionally, there is strong evidence of synergism between daratumumab and IMiDs. We therefore hypothesize that the combination of KRd plus daratumumab (KRdD), particularly in combination with auto-HCT, will be safe and lead to deep remission in a large proportion of patients with newly diagnosed MM. In fact, a phase 1 study has explored the use of KRdD in newly diagnosed MM patients and found the combination to be safe and highly active(46).

Similar to the paradigm established in other hematologic malignancies that are considered curable, the achievement of MRD(-) status is necessary for long term disease control in MM. Patients with sustained MRD(-) status may be able to undergo more abbreviated treatment and safely discontinue therapy without disease recurrence, while patients who remain MRD(+) are more likely to benefit from continuous therapy.

Therefore, this study assesses the safety and efficacy of induction therapy with KRdD, followed by auto-HCT and post-transplant KRdD consolidation, with duration of therapy determined by achievement of MRD(-) status, and treatment discontinuation in confirmed MRD (-) patients. Since continuous therapy is considered the current standard of care for patients with newly diagnosed MM, the study will assess the feasibility of monitoring for MRD resurgence ($\geq 10^{-5}$) on confirmed MRD(-) patients off therapy providing the opportunity for those subjects to proceed with SOC maintenance lenalidomide if resurgence of MRD.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To determine the frequency of MRD(-) remissions ($\leq 10^{-5}$ MM-associated molecules) after completion of intense treatment plan that consist of induction therapy, followed by consolidation therapy with a multi-drug regimen combined with continuous daratumumab therapy in patients with newly diagnosed multiple myeloma

2.2 SECONDARY OBJECTIVES

- To determine the toxicity profile of the combination of carfilzomib, lenalidomide, dexamethasone and daratumumab (KRdD) in the treatment of patients with newly diagnosed MM.

- To determine the frequency of Imaging plus MRD-negative patients ($\leq 10^{-5}$ MM-associated molecules in bone marrow and no area of PET/CT FDG uptake greater than mediastinal blood pool or surrounding normal tissue).

- To determine the frequency of MRD(-) status after induction therapy with KRdD.

- To determine the frequency of conversion from MRD(+) to MRD(-) status with auto-HCT after completion of KRdD induction.

- To determine the frequency of patients achieving complete remission (CR) with the above mentioned treatment regimen.

- To determine the feasibility and effectiveness of MRD-guided treatment discontinuation in newly diagnosed MM patients that have confirmed MRD(-).

- To determine the risk and timing of resurgence of MRD ($\geq 10^{-5}$) after discontinuation of therapy in confirmed MRD(-) patients

2.3 EXPLORATORY OBJECTIVE

- To describe PFS in cytogenetically defined high-risk patients [myeloma harboring t(4;14), t(14;16), del17p] and cytogenetically defined standard risk patients who discontinue therapy upon confirmed MRD$<10^{-5}$

.

3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

This is a Single arm, multi-center, open label phase 2 trial with safety lead in and response-adapted therapy

INDUCTION THERAPY

The maximal tolerated dose of weekly carfilzomib when administered in combination with dexamethasone, lenalidomide and daratumumab has not been determined. The dose of 56mg/m^2 was chosen as a one level dose reduction from the dose of carfilzomib utilized as single agent in the ARROW trial, therefore accounting for the possibility of added toxicity when carfilzomib is used in combination(34).

Therefore, upon approval of PA2 6 subjects were enrolled in a safety lead in cohort that received induction therapy with the following regimen, with a target dose of carfilzomib of 56 mg/m^2:

Cycle 1

Dexamethasone 40 mg PO days 1,8,15 and 22

Lenalidomide 25 mg PO daily, days 1-21

Carfilzomib 20 mg/m2 day 8; Carfilzomib 56 mg/m2 day 15

Daratumumab 16 mg/kg days 1, 8, 15 and 22

Cycle 2

Dexamethasone 40 mg PO days 1,8,15 and 22

Lenalidomide 25 mg PO daily, days 1-21

Carfilzomib 56 mg/m2 days 1, 8, and 15

Daratumumab 16 mg/kg days 1, 8, 15 and 22

Cycles 3-4

Dexamethasone 40 mg (or LTD) PO days 1,8,15 and 22

Lenalidomide 25 mg (or LTD) PO daily, days 1-21

Carfilzomib 56 mg/m2 (or LTD) days 1, 8, and 15

Daratumumab 16 mg/kg days 1,15

-If < 2 subjects experience a DLT during the first two cycles in the safety lead-in cohort, the regimen would be considered safe and enrollment would proceed with individuals being treated at the same dose level.

-If 2 or more subjects experienced a DLT during the first two cycles in the safety lead-in cohort, the study would be reviewed by the data safety monitoring board that may recommend protocol amendment.

No DLT was verified during the first 2 cycles of the initial 6 subjects enrolled under PA2. Therefore the data safety monitoring board considered the combination regimen safe and authorized subsequent enrollment.

Response assessment based on serum and urine protein electrophoresis, serum and urine immunofixation and serum free light chains will occur at the end of cycles 2 and 4 of induction. Bone marrow aspiration with MRD assay (in subjects found to be MRD-informative based on clone identification sample) will be performed at the end of cycle 4 (hereafter referred to as induction MRD).

3.1.1.1 Definition of DLT

For the safety lead-in cohort, the occurrence of any of the below toxicities during the first 2 cycles of therapy will be considered dose-limiting toxicities when definitively, probably or possibly attributed to study drug:

1) Grade 3 or 4 neutropenia (absolute neutrophil count < 1000/mm^3) with fever.

2) Grade 4 neutropenia lasting more than 7 days.

3) Grade 4 thrombocytopenia (< 25,000/mm^3) with bleeding or lasting more than 7 days.

4) Grade 4 toxicity, other than hematological toxicity.

5) Grade 3 toxicity other than hematological toxicity, fever, chills, dyspnea, rash, fatigue, flu-like syndrome, pain, anorexia, glucose intolerance, alkaline phosphatase elevation or hypertension.

6) Death from any cause.

CONSOLIDATION

Upon completion of 4 cycles of induction therapy, patients will proceed with standard of care auto-HCT, hereafter called consolidation 1. Hematopoietic progenitor cell mobilization will be performed utilizing growth-factors (G-CSF, Pegfilgrastim or similar) with or without the addition of plerixafor using standard practices at the enrolling site.

The use of chemotherapy mobilization is not allowed as it may add toxicity, delay transplant and post-transplant recovery. Chemotherapy mobilization may be employed after failure of initial mobilization attempt and after discussion with study PI.

Subjects who are transplant eligible, but choose to defer transplant, will collect hematopoietic progenitor cells and them proceed to KRdD consolidation (also labeled consolidation block 1). Subjects that are considered by the investigator not to be transplant eligible will proceed to KRdD consolidation block 1 without hematopoietic progenitor cells collection.

Auto-HCT conditioning therapy with consist of Melphalan 200mg/m^2 administered as single or divided dose on day -2 and/or -1. Supportive care following auto-HCT will follow standard of care institutional practices. Subjects will resume consolidation therapy not earlier than 90 days and ideally not later than 112 days after auto-HCT.

Subjects undergoing KRdD as consolidation block 1 will receive 4 28-day cycles consisting of:

Dexamethasone 40 mg (or LTD) PO days 1,8,15 and 22

Lenalidomide 25 mg (or LTD) PO daily, days 1-21

Carfilzomib 56 mg/m2 (or LTD) days 1, 8, and 15

Daratumumab 16 mg/kg days 1 (days 1 and 15 on the first two cycles of consolidation)

Subjects not achieving confirmed MRD(-) status during consolidation block 1 (i.e. $<10^{-5}$ on induction-MRD and consolidation-1 MRD)will undergo consolidation block 2 and, if still not confirmed MRD(-)(i.e. $<10^{-5}$ on consolidation-1 MRD and consolidation-2 MRD) they will undergo consolidation block 3. Consolidations block 2 and block 3 consist each of a block of 4 28-day cycles of KRdD as outlined:

Dexamethasone 40 mg (or LTD) PO days 1,8,15 and 22

Lenalidomide 25 mg (or LTD) PO daily, days 1-21

Carfilzomib 56 mg/m2 (or LTD) days 1, 8, and 15

Daratumumab 16 mg/kg days 1 (days 1 and 15 in the first two cycles of consolidation block 2 for patients who underwent auto-HCT as consolidation block 1)

Response assessment based on serum and urine protein electrophoresis, serum and urine immunofixation and serum free light chains will occur 60-80 days after auto-HCT and at the end of each even cycle during KRdD consolidation (for consolidations 1,2 and 3). Bone marrow aspiration with MRD assay (in subjects found to be MRD-informative based on clone identification sample) will be performed 60-80 days after auto-HCT (or on day 1 of cycle 3 of KRdD consolidation block 1 for patients not undergoing auto-HCT), hereafter referred to as consolidation-1 MRD , and, when applicable, on day 1 of cycles 3 KRdD of consolidation block 2 hereafter referred to as consolidation-2 MRD and on day 1 of cycle 3 of KRdD consolidation block 3 hereafter referred to as consolidation-3 MRD .

.

OBSERVATION/ MAINTENANCE THERAPY

Subjects will start observation/maintenance therapy after completing the entire planned consolidation therapy or after obtaining confirmed MRD(-)($\leq 10^{-5}$ MM-associated in two consecutive tests) assessment on consolidation-1 MRD, consolidation-2 MRD or consolidation-3 MRD.

3.1.3.1 MRD negative cohort

Subjects who obtain confirmed MRD(-) assessments in consolidation-1 MRD, consolidation-2 MRD or consolidation-3 MRD will be observed in the confirmed MRD(-)cohort.

Subjects will enter an active surveillance phase when they will undergo response assessment based on serum and urine protein electrophoresis, serum and urine immunofixation and serum free light chains not less often than every 8 weeks for the first 24 weeks after discontinuation of therapy and not less often than every 16 weeks afterwards. Subjects will undergo active surveillance for resurgence of MRD ($\geq 10^{-5}$) by undergoing bone marrow aspirate and MRD testing at the end of 24 and 72 weeks of observation (+/- 4 weeks).

After completion of 72 weeks of active surveillance, subjects will enter a follow up phase consisting of clinic visits, response assessment based on serum and urine protein electrophoresis, serum and urine immunofixation and serum free light chains not less often than every 16 weeks. During the follow up phase the study will capture at least once a year the occurrence of disease progression, initiation of any anti-myeloma therapy, death from any cause and any MRD assessment performed as part of routine care of the patient. This information will be submitted utilizing a follow-up form (Appendix C) at least yearly or at any time there is progression, initiation of anti-myeloma therapy, death or a new MRD assessment performed as part of routine care of the patient is reported.

3.1.3.2 MRD positive cohort

Subjects who are not evaluable for MRD status, remain MRD(+)(> 10^{-5} MM-associated molecules) or have only one MRD(-) test obtained on consolidation-3 (therefore not confirmed) will discontinue experimental therapy and be followed in the MRD(+) cohort.

In this cohort, it is suggested that patients receive standard of care lenalidomide maintenance in the follow up phase. Suggested starting dose lenalidomide is 10 mg/day continuously. Dose and schedule will be subsequently managed per treating physician. It is suggested that individuals undergo response assessment based on serum and urine protein electrophoresis, serum and urine immunofixation and serum free light chains not less often than every 16 weeks after discontinuation of experimental therapy. During the follow up phase the study will capture at least once a year the occurrence of disease progression, death from any cause, use of any anti-myeloma therapy and any MRD assessment performed as part of routine care of the patient. This information will be submitted utilizing a follow-up form (Appendix C) at least yearly or at any time there is progression, initiation of anti-myeloma therapy, death or a new MRD assessment performed as part of routine care of the patient is reported.

3.2 NUMBER OF CENTERS

UAB (P.I. Dr. Luciano Costa) will be the coordinating center for the study with participation of up to 6 additional sites.

3.3 NUMBER OF SUBJECTS

Six subjects were enrolled in the safety lead-in cohort. Additional subjects (estimated between 27 and 32), necessary for 27 MRD evaluable subjects will be enrolled in the first stage of the study. If more than 17 MRD evaluable subject reach MRD(-) status at completion of consolidation, additional subjects will be enrolled in the second stage for a total of 82 (and estimated 68 MRD evaluable) subjects in the study. As long as this experimental therapy is not declared futile at end of second stage, the study will be expanded to enroll additional 41 subjects (total 123) to enable description of PFS in HR and SR patients reaching confirmed MRD (-) and undergoing treatment discontinuation.

3.4 ESTIMATED STUDY DURATION

Accrual is expected to last 26 months. The duration of experimental treatment will be 8-16 months, depending on response and achievement of MRD. Primary endpoint will be assessed no longer than 16 months after last subject, first treatment, therefore 42 months from start of accrual. Exploratory endpoint will be assessed 24 months after last subject completes therapy, therefore up to 40 months from last subject initiating therapy.

3.5 TREATMENT SCHEMA

Screening – Subjects likely to meet eligibility criteria will be offered participation in the study after the investigator verifies UAB CTNMO registration. Subjects will sign informed consent prior to any protocol associated procedure. Screening procedures are outlined in Table 7 and will 1) ensure that subject meets all the eligibility criteria, 2) obtain disease assessment to allow efficacy measurements, 3) assess baseline toxicity, and 4) ensure initial disease sample is obtained for assessment of the myeloma-associated clone and feasibility of MRD assessment by NGS.

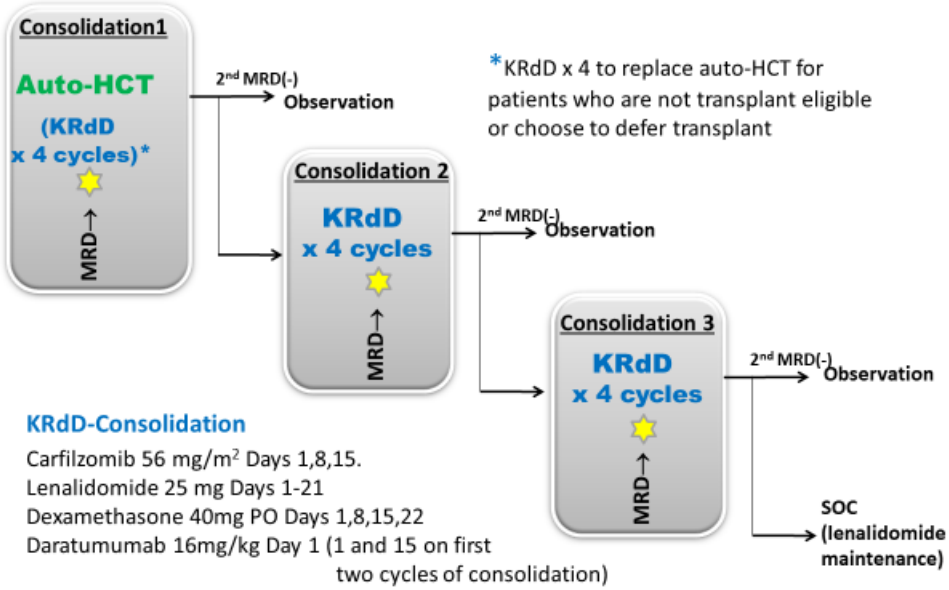
INDUCTION

KRdD- Induction

Carfilzomib 56 mg/m^2 Days 1,8,15 (omitted D1; 20 mg/m^2 D8 on C1)
Lenalidomide 25 mg Days 1-21
Dexamethasone 40mg PO Days 1,8,15,22
Daratumumab 16mg/kg Days 1,8,15,22 (C 1,2),
Day 1,15 (C3, C4)

MRD assessment by ClonoSEQ®

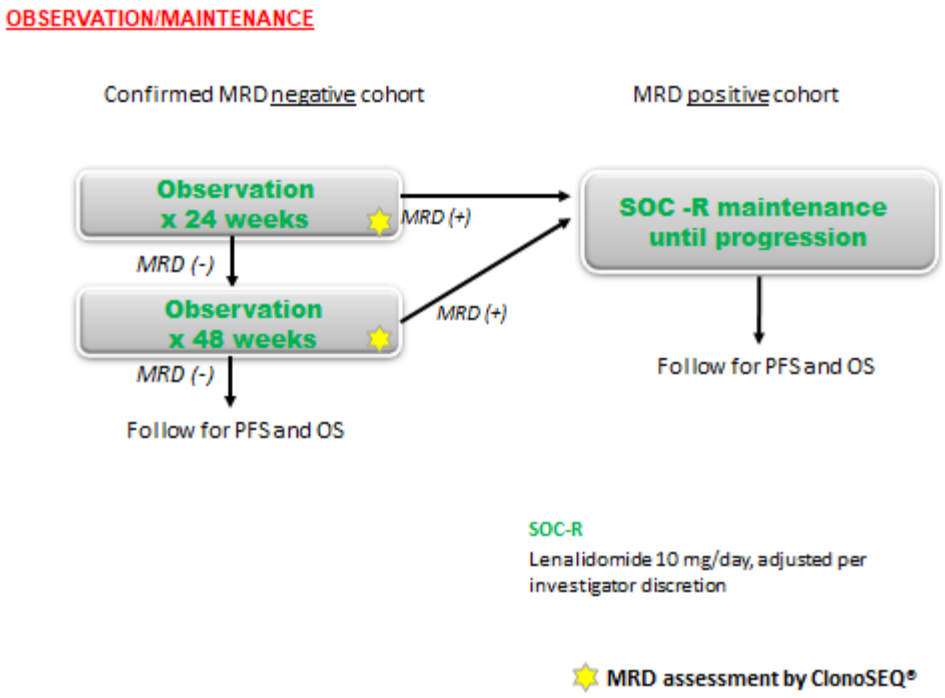
CONSOLIDATION



KRdD-Consolidation

Carfilzomib 56 mg/m^2 Days 1,8,15.
Lenalidomide 25 mg Days 1-21
Dexamethasone 40mg PO Days 1,8,15,22
Daratumumab 16mg/kg Day 1 (1 and 15 on first two cycles of consolidation)

MRD assessment by ClonoSEQ®



3.6 MINIMAL RESIDUAL DISEASE ASSESSMENTS

MRD assessment by ClonoSEQ® requires an initial marrow sample containing myeloma cells for identification of myeloma-specific sequences in IGH-VDJ, IDH-DJ and/or IGK. During screening a fresh bone marrow sample or archive, non-stained bone marrow aspirate slide ("ID sample") will be sent to Adaptive biotechnologies to be assessed for the presence of myeloma-specific sequences.

For all samples with MRD assessment, MRD will be reported quantitatively as proportion of multiple myeloma-associated sequences. For treatment assignment and clinical trial outcome reporting, we will consider MRD(-) if the burden of MM-associated molecules is < 10^{-5}.

Subjects who achieve confirmed MRD(-) status with < 10^{-5} MM associated molecules during consolidation will undergo FDG PET/CT scan prior to starting the active surveillance phase in the MRD(-) cohort. FDG PET/CT will be interpreted by the enrolling site and report

should be made available for central, consensus review. PET/CT will be considered "negative" if no area of FDG uptake greater than mediastinal blood pool or surrounding normal tissue.

TIME POINTS OF SAMPLE COLLECTION

Subjects with informative sequences found on initial "ID sample" will be considered "MRD informative" and will undergo MRD assessment at the following time points:

-At the end of 4th cycle of induction (Induction MRD)

-After recovery of auto-HCT or on the 3rd cycle of KRdD consolidation (consolidation-1 MRD)

-When applicable, on day 1 of cycles 3 of KRdD of consolidation block 2 (consolidation-2 MRD) and consolidation block 3 (consolidation-3 MRD)

-For subjects undergoing observation in the MRD(-) cohort, after 24 and 72 weeks in the observation phase.

SAMPLE COLLECTION AND SHIPMENT

At each of these time points a sample for MRD will obtained through bone marrow aspirate. Samples will be sent to Adaptive biotechnology for ClonoSEQ® testing. Samples will not be retained for future analysis.

Please refer to the Correlative Study Manual for handling and processing details.

4 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study.

1. Age >18 years with no upper age limit
2. Diagnosis of newly diagnosed multiple myeloma with indication for initiation of therapy.
3. Eastern Cooperative Oncology Group (ECOG) performance status 0–2
4. No prior MM-directed therapy except for dexamethasone (up to 160 mg) and/or bortezomib (up to 5.2 mg/m^2) and/or cyclophosphamide up to 1000 mg/m^2 administered for management of acute manifestations of MM (hypercalcemia, renal impairment, pain) for no longer than 4 weeks prior to enrollment (pre induction). If subject received any prior therapy, pretreatment parameters necessary for disease characterization and response assessment must be available.
5. Measurable disease, characterized by one of the following parameters (at screening or prior to pre induction):
    a. -Serum monoclonal (M) protein ≥ 1 g/dl by protein electrophoresis
    b. ->200 mg of M protein in the urine on 24 hour electrophoresis
    c. - Serum immunoglobulin free light chain ≥10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio
6. Available FISH report (performed locally or by third party cytogenetics laboratory) that informs absence or presence of high risk chromosome abnormalities [del17p, t(4;14) and t(14;16)]
7. Life expectancy ≥ 12 months.
8. Adequate hepatic function, with serum ALT ≤ 3.5 times the upper limit of normal and serum direct bilirubin ≤ 2 mg/dL (34 µmol/L) within 21 days prior to initiation of therapy.
9. Creatinine clearance (CrCl) ≥ 40 mL/minute within 21 days prior to start of therapy either measured or calculated using standard Cockcroft and Gault formula(available in https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc).
10. Written informed consent in accordance with federal, local, and institutional guidelines.
11. Females of childbearing potential (FCBP) must agree to ongoing pregnancy testing and to practice contraception during treatment and for 30 days after the last dose of carfilzomib. Male subjects must agree to practice contraception and refrain from donating sperm during treatment and for 90 days after the last dose of carfilzomib.
12. All subjects must agree to comply with and be enrolled in Revlimid REMS™ program.

4.2 EXCLUSION CRITERIA

Subjects must meet none of the following inclusion criteria to be eligible to enroll in this study.

1. Diagnosis of amyloidosis, POEMS, Waldenstrom's macroglobulinemia.
2. Major surgery, radiotherapy or infection requiring therapy within 14 days of starting treatment
3. Known FEV1 or cDLCO <50% of predicted.
4. Pregnant or lactating females.
5. Known human immunodeficiency virus infection.
6. Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR..
7. 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).
8. Unstable angina or myocardial infarction within 4 months prior to registration, NYHA Class II, III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker.
9. Cerebrovascular disease manifested as prior stroke at any time or TIA in the 12 months prior to initiation of therapy
10. Nonhematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas.
11. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 21 days prior to registration.
12. Known history of allergy to Captisol ® (a cyclodextrin derivative used to solubilize carfilzomib).

13. Subjects with pleural effusions requiring thoracentesis or ascites requiring paracentesis within 21 days prior to registration.
14. Contra indication or intolerance to required supportive care medications (aspirin and acyclovir).
15. Any other clinically significant medical disease or condition that, in the investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

5 SUBJECT ENROLLMENT

Once a patient is identified as a candidate for the trial the investigator will contact the UAB CTNMO registration office (205-975-5387, Fax No: 205-975-9875) prior to obtaining informed consent (safety lead in cohort only). Registration will be completed upon submission of documentation of eligibility to the registration office and issuance of a registration confirmation email.

Prior to accepting the registration, the registration office will verify the following:

- IRB approval at the registering institution.
- Patient eligibility.
- Existence of a signed consent form.
- Existence of a signed authorization for use and disclosure of protected health information.
- Pretreatment tests and procedures must be completed within the guidelines specified in the test schedule, including assessment of baseline symptoms.
- Cytogenetic risk classification if accrual is open for a specific risk group (e.g. HR) but not for another group (e.g. SR)
- Study drugs availability on site (for initial site patient only; Local site is responsible for assessing drug available for subsequent site enrollments).

6 TREATMENT PROCEDURES

6.1 DRUG PREPARATION AND ADMINISTRATION

CARFILZOMIB

- Carfilzomib for Injection is supplied as a lyophilized parenteral product in single-use vials. The lyophilized product is reconstituted with Water for Injection to a final carfilzomib concentration of 2 mg/mL prior to administration. The dose will be calculated using the subject's actual BSA at baseline. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a 2.2 m^2 BSA.
- At the discretion of the investigator, patients thought to be at particularly high risk for the development of TLS, based on high tumor burden, oral hydration will be encouraged, at least 48 hours before each dose of carfilzomib (6 to 8 cups of liquid per day) continuing up to the time of treatment.
- IV hydration will be given immediately prior to carfilzomib. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. The goal of the hydration program is to maintain robust urine output (eg, ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload. On the days the subject receives both daratumumab and carfilzomib, the infusion of daratumumab will replace the hydration to be given prior to carfilzomib.
- 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.
- Carfilzomib will be given as an IV infusion over approximately 30 minutes (±10 minutes). The dose will be administered at a facility capable of managing hypersensitivity reactions.
- Carfilzomib will be provided by Amgen.

LENALIDOMIDE

- Lenalidomide (revlimid®) is a thalidomide analogue immunomodulatory agent . Lenalidomide is a off-white to pale-yellow solid powder. It is solube in organic solvent/water mixtures, and buffered aqueous solvents.
- Lenalidomide is available as 5, 10, 15 and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscalmellose sodium, and magnesium stearate.
- Lenalidomide is considered standard of care for initial management of multiple myeloma, will be acquired commercially and not provided by the sponsor (University of Alabama at Birmingham).
- In order for subjects to have access to Lenalidomide, enrollment in Lenalidomide REMS is required.

DARATUMUMAB

- Infusion solution will be prepared as a 1000ml (first infusion) or 500-mL (subsequent infusions) dilution of daratumumab in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion.
- Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump. The study drug must be filtered by using an inline filter (0.2 μM) during the infusion.
- Daratumumab will be administering at 16mg/kg with subject weight rounded to the nearest kilogram. Infusion rates will follow parameters as follows (Table 1):

Table 1- Infusion parameters for daratumumab

	Dilution volume	Initial Infusion rate	Rate increment	Maximum rate
First infusion. 16mg/kg	1000 ml	50 ml/hour for 1 hour	50 ml/hour, every hour	200 ml/hour
Second infusion[a]. 16 mg/kg	500 ml	50 ml/hour for 1 hour	50 ml/hour, every hour	200 ml/hour
Subsequent infusion[b]. 16mg/kg	500 ml	100 ml/hour	50 ml/hour, every hour	200 ml/hour
Cycle 2 and beyond[c,d] (rapid infusion protocol)	500 ml	200 ml/h for 30 min (20% of dose)	400 ml/h for remaining of infusion (80% of dose)	400 ml/hour

a-Escalate only if there were no grade 1 or greater infusion reactions during the first 3 hours of the first infusion. Otherwise repeat "first infusion" sequence.

b-Escalate only if there were no grade 1 or greater infusion reactions during a final infusion rate ≥ 100mL/hr in the prior two infusion

c- For institutions using daratumumab rapid infusion protocol as their standard of care(47), rapid infusions may be considered for Cycle 2 and subsequent infusions ONLY for patients who tolerate Cycle 1 Day 22 without any grade (grade 1 or greater) hypersensitivity reaction, subsequent daratumumab infusions can be administered at an initial rate of 20% of the total dose over 30 minutes, followed by the remaining 80% of the total dose over 60 minutes (90-minute total infusion time).

d-If a patient experiences any grade hypersensitivity reaction, the patient is not eligible to receive additional rapid infusions until they have received standard infusion daratumumab without any grade hypersensitivity reaction.

- Required preinfusion medication will consist of dexamethasone 20 mg IV (or lower dose if dexamethasone has been dose reduced due to toxicity. Dose should not be less than 8 mg), acetaminophen 650 to 1000 mg PO and an antihistamine given IV or PO (diphenhydramine 25 to 50 mg or equivalent).

- Any period equal or greater than 60 days without daratumumab administration (e.g for stem cell transplantation) will require subsequent dose to be administer per first infusion parameters with advancement in rate of subsequent infusions as described in Table 1.
- Daratumumab will be provided by Janssen Scientific Affairs.

6.1.4 DEXAMETHASONE

- Dexamethasone is a synthetic adrenocortical steroid. It is available commercially in 4 mg tablets for oral administration. Each tablet contains dexamethasone as the active ingredient, and the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch.
- During clinical trial participation individuals will take dexamethasone in the dose and scheduled indicated in 3.1. Dexamethasone will be taken preferentially in the morning with food. On the days the subject will receive daratumumab administration, and consequently dexamethasone preinfusion, the dexamethasone preinfusion dose should be deducted from the oral dose to be taking assuming 1:1 equivalence between oral and IV formulation. For example, if subject is to take 40 mg of dexamethasone on that day, but is receiving 20 mg IV as preinfusion medication, then the oral dose will be of 20 mg. If dose of dexamethasone has been reduced to less than 20 mg, and patient is due for a dose of dexamethasone on same day of daratumumab infusion, the entire dose will be administered intravenously as pre infusion medication (dose should not be less than 8 mg).
- Dexamethasone is commercially available and will not be provided by the sponsor (University of Alabama at Birmingham).

MELPHALAN

- Melphalan is commercially available and supplied as a sterile, freeze-dried powder. Each vial contains 50 mg melphalan hydrochloride and the inactive ingredient, povidone 20 mg. Reconstitute per manufacturer instructions using the diluent provided. Further dilution

and administration per institutional standards. The manufacturer recommends completion of administration of melphalan within 60 minutes of reconstitution.

- The dose (200 mg/m^2) will be calculated using the lesser of the subject's actual (AW) or corrected ideal body weight (CIBW). CIBW= IBW + 0.25(AW-IBW). The ideal body weight (IBW) is calculated using the formula: Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet. Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.
- Solution Preparation: Vial/50 mg: Constitute with 10 ml of the special diluent to yield a 5 mg/ml melphalan concentration. May be further diluted per institutional guidelines.
- Melphalan must be infused intravenously utilizing a central vein catheter and infusion completed within one hour of reconstitution.
- IV hydration will be given immediately after melphalan per institutional guidelines.
- Intravenous melphalan is commercially available and will not be provided by the sponsor (University of Alabama at Birmingham).

6.2 DOSE MODIFICATIONS/ADJUSTMENTS

All toxicity assessments and dose reductions will be performed utilizing common terminology criteria for adverse events version 4.03 (CTCAE v.4.03) available in **http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf**

CARFILZOMIB

Dose reductions for toxicities that, according to investigator are definitively, probably or possibly related to carfilzomib will follow Table 2. Omitted doses will not be replaced. Patients who interrupt therapy due to toxicity will resume therapy as outlined in Table 3 receiving any remaining doses on the ongoing cycle. If no remaining doses on the current cycle, then treatment will resume after the cycle is completed, 28 (+/- 2) days from the initiation of the prior cycle.

Table 2 – Carfilzomib dose modifications

Hematologic toxicity	CTCAE v4.03 grade	Action
Thrombocytopenia	Grade 3	Hold carfilzomib and check platelet count weekly until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 3 weeks, reduce dose.
	Grade 4 or bleeding	First or second occurrences - Hold carfilzomib and check platelet count weekly until resolution to grade ≤ 2 and no bleeding. Resume therapy at one level dose reduction. Third occurrence- Discontinue drug
Anemia	Grade 3	Hold carfilzomib and check hemoglobin weekly until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose.
	Grade 4 or transfusion requirement	First or second occurrences - Hold carfilzomib and check hemoglobin weekly until resolution to grade ≤ 2. Resume therapy at one level dose reduction Third occurrence- Discontinue drug.

Neutropenia	Grade 3 or 4	Hold carfilzomib and check neutrophil count weekly until resolution to grade ≤ 2 (growth factor use is permitted), then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose.
	Grade 4 with fever or infection	First or second occurrences - Hold carfilzomib and check neutrophil count at least weekly until resolution to grade ≤ 2 (growth factor use is permitted) and no signs of infection. Resume therapy at one level dose reduction Third occurrence- Discontinue drug.
Non-hematologic toxicity	**CTC 4.0 grade**	**Action**
Cardiac Toxicity new onset or worsening of congestive heart failure;decreased left ventricular function or myocardial ischemia	Grades 3 or 4,	Withhold drug until resolved or returned to baseline. After resolution, consider if restarting carfilzomib at a reduced dose is appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician
Pulmonary hypertension	Grades 2-4	Withhold drug until resolved or returned to baseline. After resolution, consider if restarting carfilzomib at a reduced dose is appropriate. If tolerated, the reduced dose may be escalated to

		the previous dose at the discretion of the physician
Other pulmonary	Grades 3 or 4	Withhold drug until resolved or returned to baseline. After resolution, consider if restarting carfilzomib at a reduced dose is appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician
Posterior Reversible Encephalopathy Syndrome (PRES)	Any	If PRES is suspected, hold carfilzomib. Consider evaluation with MRI for onset of symptoms suggestive of PRES. If PRES is confirmed, permanently discontinue carfilzomib. If PRES is excluded, may resume carfilzomib at same dose if clinically appropriate. If PRES recurs, permanently discontinue carfilzomib
Thrombotic microangiopathy	Any grade	If TMA is suspected, hold carfilzomib and manage per standard of care. If TMS is confirmed and related to carfilzomib, permanently discontinue carfilzomib. If TMA is excluded, may restart carfilzomib.
Progressive multifocal leukoencephalopathy (PML)	Any grade	If PML is suspect, hold carfilzomib and proceed immediately with diagnostic work up, including consultation with a neurologist. Do not resume carfilzomib until PML is unequivocally excluded. If PML can not be unequivocally excluded, discontinue carfilzomib permanently.

Hepatic Impairment	Mild to moderate liver dysfunction defined as 2 consecutive values, at least 28 days apart of: total bilirubin (>33% direct > 1x ULN to < 3x ULN OR an elevation of AST and/or ALT with normal bilirubin	25% dose reduction. Dose may be re-escalated if liver function tests return to normal and drug-induced hepatotoxicity is excluded.
	Grade 3 elevation in ALT and/or AST (>5xULN)	Hold carfilzomib until resolution to baseline. Monitor any abnormality weekly. Resume carfilzomib with a 25% dose reduction if drug-induced hepatoxicity is excluded.
	Grade 3 elevation in total bilirubin	Hold carfilzomib until resolution. Monitor total bilirubin and direct bilirubin weekly. Upon resolution of total bilirubin to normal, reduce carfilzomib dosing with a 25% dose reduction if drug induced hepatoxicity is excluded.
	Drug induced hepatoxicity attributable to carfilzomib	Discontinue carfilzomib

Any other	Grades 2	No action is required. Investigator is allowed to hold study drug for up to two weeks and then resume at same dose. On second occurrence, the investigator has the option to resume therapy at reduced dose.
	Grade 3	Hold carfilzomib until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 3 weeks, reduce dose.
	Grade 4	First or second occurrence - Hold carfilzomib until resolution to grade ≤ 2. Resume therapy at one level dose reduction. Third occurrence- Discontinue drug.

Table 3- Dose levels for carfilzomib

Dose level	**Dose**
0 (zero) or safety lead-in dose	56 mg/m^2
-1 (minus 1)	45 mg/m^2
-2 (minus 2)	36 mg/m^2
-3 (minus 3)	Discontinue agent

As a subject advances through phases of therapy (induction, consolidation) the dose of carfilzomib utilized will never be higher than the last previously tolerated dose (LTD)

6.2.2 LENALIDOMIDE

Dose reductions for toxicities that, according to investigator are definitively, probably or possibly related to lenalidomide will follow Table 4. Omitted doses will not be replaced. Patients who interrupt therapy due to toxicity will resume therapy as outlined in Table 5 receiving any remaining doses on the ongoing cycle. If no remaining doses on the current cycle, then treatment will resume after the cycle is completed, 28 (+/- 2) days from the initiation of the prior cycle.

Table 4 – Lenalidomide dose modifications

Hematologic toxicity	**CTCAE v4.03 grade**	**Action**
Thrombocytopenia	Grade 3	Hold lenalidomide and check platelet count weekly until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose by one level.
	Grade 4 or bleeding	First and second occurrence - Hold lenalidomide and check platelet count weekly until resolution to grade ≤ 2 and no bleeding. Resume therapy at one level dose reduction. Second occurrence- Discontinue drug
Anemia	Grade 3	Hold lenalidomide and check hemoglobin weekly until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose.

	Grade 4 or transfusion requirement	First or second occurrence - Hold lenalidomide and check platelet count weekly until resolution to grade ≤ 2. Resume therapy at one level dose reduction Third occurrence- Discontinue drug.
Neutropenia	Grade 3 or 4	Hold lenalidomide and check neutrophil count weekly until resolution to grade ≤ 2 (growth factor use allowed), then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose.
	Grade 4 with fever or infection	First or second occurrence - Hold lenalidomide and check neutrophil count at least weekly until resolution to grade ≤ 2 (growth factor use allowed) and no signs of infection. Resume therapy at one level dose reduction Third occurrence- Discontinue therapy.
Non-hematologic toxicity	**CTC 4.0 grade**	**Action**
Any	Grades 2	No action is required. Investigator is allowed to hold study drug for up to two weeks and then resume at same dose. On second occurrence, the investigator has the option to resume therapy at reduced dose.
	Grade 3	Hold therapy until resolution to grade ≤ 2, then resume at the same dose. If toxicity lasts more than 2 weeks, reduce dose by one level.

	Grade 4	First or second occurrences - Hold lenalidomide until resolution to grade ≤ 2. Resume therapy at one level dose reduction. Thirds occurrence- Discontinue drug.

Table 5 -Lenalidomide dose levels and adjustment according to renal function.

Dose level	Induction and consolidation, part of KRdD		Standard of care maintenance for subjects in the MRD(+) cohort (suggested)	
	CrCl ≥ 60ml/min	*CrCl< 60ml/min*	*CrCl ≥ 60ml/min*	*CrCl< 60ml/min*
0	25 mg/day	10mg/day	10mg/day	5 mg/day
-1	15 mg/day	5 mg/day	5 mg/day	5 mg every other day
-2	10 mg/day	5 mg every other day	discontinue	discontinue
-3	5 mg/day	discontinue	discontinue	discontinue
-4	discontinue	discontinue	discontinue	discontinue

As a subject advances through phases of therapy (induction, consolidation, maintenance) the dose of lenalidomide utilized will never be higher than the last previously tolerated dose (LTD)

DEXAMETHASONE

Dose reductions for toxicities that, according to investigator are definitively, probably or possibly related to dexamethasone will follow Table 6. Omitted doses will not be replaced. Patients who interrupt therapy due to toxicity will resume therapy as outlined in Table 6 receiving any remaining doses on the ongoing cycle. If no remaining doses on the current cycle, then treatment will resume after the cycle is completed, 28 (+/- 2) days from the initiation of the prior cycle.

Table 6 – Dexamethasone dose modification

Toxicity	**CTCAE v4.03 grade**	**Action**
Gastrointestinal	Grades 1-2	Treat with proton pump inhibitor. Dose reduction to 20 mg/dose allowed. Dose increase to 40 mg/dose allowed once symptoms resolved.
	Grades 3 or 4	Hold dexamethasone and treat with proton pump inhibitor. Once symptoms resolve or improve to grade 1, resume at a dose not greater than 20 mg/dose. Consider additional dose reductions if recurrence of symptoms. Dose increase not allowed. If multiple recurrences of grade 3 or 4 gastrointestinal toxicity despite concomitant medication and dose reduction, discontinue dexamethasone and do not resume, except for the minimal dose of 8 mg as pre infusion prior to daratumumab.
Cardiovascular	Edema grades 3 or 4	Hold dexamethasone and treat with diuretics as needed. Once symptoms resolve or improve to

		grade 1, resume dexamethasone at a dose not greater than 20 mg/dose. Consider additional dose reductions if recurrence of symptoms. Dose increase not allowed. If multiple recurrences of grade 3 or 4 edema despite concomitant medication and dose reduction, discontinue dexamethasone and do not resume, except for the minimal dose of 8 mg as pre infusion prior to daratumumab.
Neurologic or psychiatric	≥ grade 2	Hold dexamethasone until symptoms resolve. Consider consultation with specialist and pharmacologic treatment. Once symptoms resolved, resume dexamethasone at dose not higher than 20 mg/dose. Consider additional dose reductions if recurrence of symptoms
Other	Grades 3 or 4	Hold dexamethasone. Once symptoms resolve or improve to grade 1, resume at a dose not greater than 20 mg/dose. Consider additional dose reductions if recurrence of symptoms Dose increase not allowed. If multiple recurrences of grade 3 or 4 toxicity despite concomitant medication and dose reduction, discontinue dexamethasone and do not resume, except for the minimal dose of 8 mg as pre infusion prior to daratumumab.

DARATUMUMAB

There will be no dose modification (increase or decrease) for daratumumab. Any dose hold for greater than 28 days due to toxicity will result in permanent discontinuation of daratumumab.

Daratumumab dosing will be held if any of the following adverse events is present.

Febrile neutropenia

Grade 4 hematologic toxicity

Any grade 3 or 4 non-hematologic toxicity that the investigator considers definitively, probably or possibly caused by daratumumab. Daratumumab will be resumed when toxicity resolved to ≤ grade 2.

MELPHALAN

Melphalan will be administered as standard of care, single dose, conditioning regimen in preparation for auto-HCT. The recommended dose is 200mg/m2. Dose adjustments according to age or renal function will follow each participating site's standards.

6.3 SAFETY CONSIDERATIONS

- 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 the following day, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release.

- Carfilzomib will be generally administered on the same day of daratumumab administration. Carfilzomib should be administered after completion of daratumumab administration. Therefore, subjects will have received 20 mg of dexamethasone as premedication prior to daratumumab. In the event of patient receiving carfilzomib but not daratumumab in a given day, dexamethasone at least 4 mg IV will be administered prior to carfilzomib.

- Should a "first dose carfilzomib effect" occur, 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 for immediate use and instituted, as medically indicated.

- CrCl changes induced by carfilzomib are mostly transient, reversible, and non-cumulative. All subjects should be well hydrated. Clinically significant electrolyte abnormalities should be corrected prior to dosing with carfilzomib. 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. Carfilzomib must be held for subjects with a CrCl < 15 mL/min at any time during study participation.

- Carfilzomib is associated with increased risk of cardiac events that are, at least in part, linked to increase in blood pressure. Intense blood pressure monitoring is required for patients being treated with carfilzomib. All subjects will receive a blood pressure monitoring log where daily blood pressure measurements will be recorded. The log will be reviewed at each clinical visit and hypertension will be actively managed by the investigator

- Subjects with active or suspected infection of any kind that required systemic treatment should not be dosed with carfilzomib, lenalidomide or daratumumab until the infection has resolved (and preferentially the course of antibiotics has been completed).

- Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetic or antidiarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration.

- Lenalidomide, a thalidomide analogue, can cause limb abnormalities. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment.

- Lenalidomide is associated with increase in risk of venous and arterial thromboembolism. Anti-thrombotic prophylaxis with aspirin or anticoagulation is required.
- Lenalidomide can impair stem cell mobilization. Stem cell collection is recommended after no more than 4 cycles of therapy containing lenalidomide for subjects who are consider adequate candidates for hematopoietic progenitor cell transplantation.
- Daratumumab is associated with risk of infusion-related reactions (mostly fever, cough, dizziness, bronchospasm) in approximately 40% of patients. These reactions are mostly grades 1 and 2 and occur during first infusion. See guidelines for management of daratumumab infusion-related reactions in 6.3.2.
- The treatment with melphalan as outlined in this protocol constitutes standard of care. The dose of 200mg/m^2 of melphalan is myeloablative, therefore subjects are expected to develop grade 4 thrombocytopenia requiring transfusion, grade 4 neutropenia with near 100% risk of neutropenic fever and anemia requiring transfusion of red blood cells.
- Melphalan at the doses employed in this protocol will cause nausea, vomiting and mucositis manifested mostly as oral pain, dysphagia and diarrhea. Subjects will receive antiemetic and antidiarrheal medications according to institutional guidelines.

6.3.1 GUIDELINES FOR MONITORING, PROPHYLAXIS, AND TREATMENT OF TUMOR LYSIS SYNDROME (TLS)

TLS, which may be associated with multiorgan failure, has been observed in some patients with MM who have been treated with carfilzomib, lenalidomide and dexamethasone, alone or in combination, during first or second cycles of therapy.

The following safety measures are mandatory for all subjects. In addition, MM subjects with high tumor burden (e.g., Durie-Salmon or ISS Stage II/III) or rapidly increasing M-protein or light chains or compromised renal function (CrCl < 50 mL/min) should be considered to be at particularly high risk. Please see section 6.1.1 for hydration requirements.

6.3.1.1 Laboratory Monitoring

Appropriate chemistries, including creatinine and complete blood counts (CBC) with platelet count, should be obtained and reviewed prior to carfilzomib dosing. Results of laboratory studies must be reviewed and deemed acceptable prior to administering the carfilzomib dose. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, LDH ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose. Subjects with such abnormalities should be re-evaluated again within the next 24 hours (or sooner, if clinically indicated) and then periodically as clinically indicated.

6.3.1.2 Management of Tumor Lysis Syndrome

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

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

6.3.2 GUIDELINES FOR MONITORING, PROPHYLAXIS, AND TREATMENT OF DARATUMUMAB INFUSION-RELATED REACTION (IRR)

Daratumumab infusion-related reactions occur in approximately 40% of patients receiving first dose of daratumumab. Most reactions are grade 1 or 2, but serious, including life-threatening reactions have occurred.

Common manifestations of IRR are pyrexia, cough, bronchospasm, dizziness, urticaria reduction in blood pressure.

6.3.2.1 Prevention

All patients receiving daratumumab will receive preinfusion medication consisting of:

- Dexamethasone 20 mg IV;

- Acetaminophen 650 to 1000 mg PO
- Antihistamine given IV or PO (diphenhydramine 25 to 50 mg or equivalent).
- Montelukast 10 mg PO the day before and day of infusion.

For subjects with a higher risk of respiratory complications, the following postinfusion medications should be considered:

- Antihistamine given IV or PO (diphenhydramine 25 to 50 mg or equivalent) on the first and second day after all the infusions
- Short-acting beta 2 adrenergic receptor agonists such as salbutamol aerosol.

6.3.2.2 Management of infusion-related reactions

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available at bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time. If an infusion-related reaction develops, then the infusion should be temporarily interrupted or slowed down. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. The following guidelines apply:

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be

discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.

- If an infusion is paused or the infusion rate is decreased, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as serious adverse events.
- For IRR grades 1 and 2 the then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion. If the subject 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 subject must be withdrawn from treatment.
- For IRR grade 3 or higher the infusion must be stopped and the subject must be observed carefully until resolution of the adverse event. If the intensity of the adverse event decreases to Grade 1 or 2 within 2 hours, then the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

6.4 CONCOMITANT MEDICATIONS

Concomitant medication is defined as any prescription or over-the-counter preparation including vitamins and supplements. Concomitant medications should be recorded from 14 days before Day -3 through the end of the subject's study participation. Any change in concomitant medications must be recorded.

REQUIRED CONCOMITANT MEDICATIONS

Female subjects of child-bearing potential must agree to use dual methods of contraception for the duration of the study. Male subjects must agree to use a barrier method of contraception for the duration of the study if sexually active with a female of child-bearing potential. All subjects in the study are required to be enrolled in and compliant with revlimid REMS®

Dexamethasone at least 4 mg PO/IV will be administered prior to all carfilzomib doses.

All subjects will receive prophylaxis against herpes zoster. Recommended agents and doses are acyclovir 400 mg PO twice a day or valacyclovir 500 mg PO daily.

All patients will receive prophylaxis for Pneumococcal disease. Recommended agents and doses are Penicillin 500 mg PO twice a day or doxycycline 100 mg PO twice a day

All subjects will receive prophylaxis against thromboembolic events while on therapy with lenalidomide and/or carfilzomib with Aspirin 325 mg/day, low-molecular weight heparin,or oral anticoagulants according to risk-strata as outlined in the International Myeloma Working Group guideline (48).

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation. see Section 4.2. For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

6.4.2 OPTIONAL AND ALLOWED CONCOMITANT MEDICATIONS

Allopurinol (in subjects at risk for TLS due to high tumor burden) is optional and will be prescribed at the Investigator's discretion.

Biphosphonate therapy, per institutional guidelines, is allowed and encouraged.

Vitamins and supplements should be recorded on the concomitant medication page. All transfusions and/or blood product related procedures must be recorded on the appropriate form.

6.4.3 EXCLUDED CONCOMITANT MEDICATIONS

Concurrent therapy with an approved or investigative anticancer therapeutic with activity against multiple myeloma is not allowed. Other investigative agents (e.g., antibiotics or antiemetics) should not be used during the study.

7 STUDY TESTS AND OBSERVATIONS

Table 7 – Study enrolment, induction therapy and study evaluations.

	Screening	**Cycle 1**				**Cycle 2**				**Cycles 3 and 4**			
	21 days from onset of therapy	Protocol day				Protocol day				Protocol day			
		1	8	15	22	1	8	15	22	1	8	15	22
History and Physical	X	X				X				X			
Vitals	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X				X				X			
Height	X												
Skeletal survey	X												
Complete blood counts	X	X	X	X	X	X	X	X	X	X		X	
Metabolic panel (Na, K, Cr, BUN, Cl, Bicarbonate, glucose)	X	X	X	X	X	X	X	X	X	X		X	
Calcium, Phosphorus, Uric acid	X	X	X	X		X	X	X		X			
Total bilirubin, AST, ALT, alkaline phosphatase, LDH,	X	X	X	X		X	X	X		X			
B2 microglobulin	X												
Hepatitis B virus (HBV) core antibody, HBV surface antigen, HBV surface antibody	X												
HBV DNA	X[6]									X[7]			
Echocardiogram	X												
Electrocardiography	X												
Serum protein electrophoresis	X									X[4]			
24h urine protein electrophoresis	X									X[3,4]			
Serum free light chains	X									X[4]			
Serum and urine Immunofixation	X									X[4]			
Bone marrow aspiration and biopsy[1]	X												

Adverse Events Assessment[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications Review	X	X				X				X			
Serum pregnancy test, if appropriate	X	X				X				X			
Confirmation of enrollment in Revlimid REMS®	X	X				X				X			
Carfilzomib infusion			X	X		X	X	X		X	X	X	
Lenalidomide treatment[2]		X[2]	X[2]	X[2]		X[2]	X[2]	X[2]		X[2]	X[2]	X[2]	
Dexamethasone treatment		X	X	X	X	X	X	X	X	X	X	X	X
Daratumumab infusion		X	X	X	X	X	X	X	X	X		X	

1-This assessment will include morphology, flow cytometry, FISH for myeloma-associated abnormalities and sample to be sent to Adaptive biotechnology for identification of myeloma-specific sequences (see section 3.6). If subject has already had a diagnostic bone marrow aspiration and biopsy this is not necessary as long as the enrolling site can verify that there is adequate FISH information and enough and adequate sample in storage to be sent to Adaptive biotechnologies for identification of myeloma-specific sequences

2 – Lenalidomide treatment daily from days 1-21.

3- Necessary only when M spike in urine is main parameter for response assessment.

4- On cycle 3 day 1 only.

5-Continuously

6- For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. HBV DNA not necessary for patients positive for anti-HBs, but negative for Anti-HBc and with a history of hepatitis B vaccination.

7- Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment

Table 8 – Consolidation therapy and study evaluations.

	Prior to consolidation	**Subjects on auto-HCT for consolidation 1**			**Subjects on KRdD for consolidation 1, cycles 1-4**				**Consolidation 2,3, cycles 1-4 of each block**			
	14 days from onset of therapy or mobilization[4]	Protocol day			Protocol day				Protocol day			
		-2 or -1	0	60 to 80	1	8	15	22	1	8	15	22
History and Physical		X		X	X				X			
Vitals		X		X	X	X	X		X	X	X	
Weight		X		X	X				X			
Complete blood counts	X			X	X		X		X		X	
Metabolic panel (Na, K, Cr, BUN, Cl, Bicarbonate)	X			X	X		X		X		X	
Total bilirubin, AST, ALT, alkaline phosphatase	X			X	X				X			
HBV DNA				X[11]	**X[11]**				**X[11]**			
Serum protein electrophoresis	X			X	X[7]				X[7]			
24h urine protein electrophoresis	X[3]			X[3]	X[3]				X[3,7]			
Serum free light chains	X			X	X[7]				X[7]			
Serum and urine Immunofixation	X			X	X[7]				X[7]			
Bone marrow aspiration[1]	X			X	X[5]				X[6]			
Adverse Events Assessment[8]		X		X	X	X	X	X	X	X	X	X
Blood pressure monitoring				X	X	X	X	X	X	X	X	X
Concomitant Medications Review		X		X	X				X			
Serum pregnancy test, if appropriate				X	X				X			
Confirmation of enrollment in Revlimid REMS®				X	X				X			
Melphalan infusion		X										

Hematopoietic progenitor cells infusion			X									
Carfilzomib infusion					X	X	X		X	X	X	
Lenalidomide treatment[2]					X[2]	X[2]	X[2]		X[2]	X[2]	X[2]	
Dexamethasone treatment					X	X	X	X	X	X	X	X
Daratumumab infusion					X		X[9]		X		X[10]	

1- Sample to be provided for MRD assessment (see section 3.6).
2 – Lenalidomide treatment daily from days 1-21.
3- Necessary only when M spike in urine is main parameter for response assessment.
4- May overlap with cycle 4 of induction
5- Bone marrow aspiration with MRD assay (in subjects found to be MRD-informative based on clone identification sample) will be performed on day 1 of cycle 3 of KRdD consolidation 1 for patients not undergoing auto-HCT.
6- Bone marrow aspiration with MRD assay (in subjects found to be MRD-informative based on clone identification sample) will be performed on day 1 of cycle 3 of KRdD consolidation 2 and, when applicable, on day 1 of cycle 3 of KRdD consolidation 3.
7- To be performed on day 1 of cycles 1 and 3.
8- Continuously
9- Only on cycles 1 and 2 of consolidation block 1.
10- Only on cycles 1 and 2 of consolidation block 2 and only for patients who underwent auto-HCT as consolidation 1.
11- For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment. HBV DNA not necessary for patients positive for anti-HBs, but negative for Anti-HBc and with a history of hepatitis B vaccination.

Table 9 – Observation/Maintenance therapy and study evaluations.

	MRD negative cohort					**MRD positive cohort**
	Active surveillance phase				Follow up phase	Follow up
	Anytime during first 3 weeks	Wk, 24 from EOT[4]	Wk. 72 from EOT[4]	Ever 8 weeks[5] during wks 1-24, every 16 wks[4] afterwards	Every 16 wks[5] after active surveillance phase	Every 16 wks[4]
History and Physical				X	X	X
Vitals				X	X	X
Complete blood counts				X	X	X
Metabolic panel (Na, K, Cr, BUN, Cl, Ca, Bicarbonate)				X	X	X
Total bilirubin, AST, ALT, alkaline phosphatase, LDH				X	X	X
HBV DNA				X[6]		
Serum protein electrophoresis				X	X	X
24h urine protein electrophoresis				X[3]	X[3]	X[3]
Serum free light chains				X	X	X
Serum and urine Immunofixation				X	X	X
Bone marrow aspiration[1]		X	X			
FDG PET/CT scan	X					
Adverse Events Assessment				X		
Concomitant Medications Review				X		
Serum pregnancy test, if appropriate						X
Confirmation of enrollment in Revlimid REMS®						X
SOC Lenalidomide treatment[2]						X[2]

1- Sample to be provided for MRD assessment (see section 3.6).
2 –Lenalidomide treatment daily from days 1-28 is suggested, but not required
3- Necessary only when M spike in urine is main parameter for response assessment.
4-+/- 4 weeks- suggested timeline
5-+/- 4 weeks
6- Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment. HBV DNA not necessary for patients positive at screening for anti-HBs, but negative for Anti-HBc and with a history of hepatitis B vaccination.

8 STUDY, TREATMENT AND PARTICIPATION DISCONTINUATION

8.1 REASONS FOR STUDY DISCONTINUATION

Reasons for study discontinuation may include, but are not limited to:

- Safety concerns as indicated by investigator or DSMB.
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

8.2 REASONS FOR TREATMENT DISCONTINUATION

Reasons for subject discontinuation of study treatment are:

- Confirmed progressive disease (appendix B)
- Toxicity that in the opinion of investigator or DSMB is not adequately controlled and/or recurrent despite necessary dose modifications are outlined in section 6.2.
- Discontinuation of subject participation in the study.

8.3 REASONS FOR STUDY PARTICIPATION DISCONTINUATION

Reasons for subject discontinuation of study participation are:

- Withdraw of consent.
- Any reason that in the opinion of the investigator, DSMB or IRB makes the subject participation in the study unfeasible or unsafe

9 ADVERSE EVENTS

9.1 OVERVIEW

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

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

9.2 MANAGEMENT OF SAFETY DATA

This Study has been designated as an interventional study. As such, all adverse events, special situations including pregnancies and product quality complaints for J&J Medicinal Product and for Amgen Medicinal Product regardless of causality and special situations excluding those from subjects not exposed to a J&J medicinal product and/or Amgen medicinal product, quality complaints with or without an adverse event as described in this protocol will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last documented use of product under study within the study. All subsequent AEs and SAEs will be collected after this period if the Principal Investigator considers the AE/SAE to be causally-related to the study drug.

For the purposes of this study, the Janssen medicinal product is:
DARZALEX®(daratumumab)

For the purposes of this study, the Amgen medicinal product is: KYPROLIS® (carfilzomib)

9.3 ADVERSE EVENTS DEFINITIONS

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

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

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current IB or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered “unexpected”.

Whenever possible, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 should be used to describe the event and for assessing the severity of AEs (see Appendix A). Any events representing a change in the CTCAE Grade need to be reported on the AE case report form. This includes any change in laboratory values.

For AEs not adequately addressed in the CTCAE, the severity Table 10 below may be used:

Table 10- Adverse Event Severity

Severity	Description
GRADE 1 – Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
GRADE 2 – Moderate	Moderate; minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
GRADE 3 – Severe	Severe or medically significant but not life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care ADL.
GRADE 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated.
GRADE 5 – Fatal	Death related to AE.

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

9.4 CAUSALITY

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows:

Yes: The event is suspected to be related if:

- there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
- there is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
- the event responds to withdrawal of the study medication (dechallenge) and/or recurs with rechallenge (when clinically feasible); and/or
- the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures

No:

- the AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure; and/or

- the time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
- the event is unlikely to be related to the investigational product(s)

9.5 ADVERSE EVENTS OF SPECIAL INTEREST (DARATUMUMAB)

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

- Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- HBV reactivation
- Other malignancies

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

9.6 UNLISTED (UNEXPECTED ADVERSE EVENTS/REFERENCE SAFETY INFORMATION

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

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

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

9.7 ADVERSE EVENTS REPORTING PROCEDURES

All AEs (e.g., any new event or worsening in severity or frequency of a pre-existing condition or laboratory finding) with an onset date after the subject signs consent for study participation must be promptly documented on the appropriate summary. Details of the event must include severity, relationship to study drug, duration, action taken, and outcome. Serious adverse events (SAEs) will be recorded on the appropriate form.

All AEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected.

AEs should be reported from the time the subject signs consent through 30 days post-last dose of study drug or initiation of a new anti-cancer therapy, whichever occurs first. In addition, the Investigator should report any AE that may occur after this time period that is believed to have a reasonable possibility of being associated with study drug. If a subject is registered but discontinues the study prior to receiving any study drug, AEs must be reported through the end-of-study visit. AEs which completely resolve and then recur should be recorded as a new AE. For subjects who complete the end of study visit less than 30 days following their last dose of study drug, a follow up of ongoing AEs should be attempted by telephone and documented in the subject's source document. AEs continuing at 30 days post-last dose should have a comment in the source document by the Investigator that the event has stabilized or is not expected to improve.

The experimental approach encompassed in this protocol governs induction therapy and post auto-HCT consolidation and maintenance therapy. Auto-HCT itself is standard of care treatment with well known toxicity profile. Therefore AEs that occur after initiation of auto-HCT and before initiation of post auto-HCT consolidation are not reportable unless they occur within 30 days of last dose of carfilzomib, daratumumab or lenalidomide.

The Principal Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. Adverse events will be assigned a severity grade using the NCI-CTCAE grading scale v4.0.

All Grade 3 and 4 adverse events must be recorded as AEs on the CRF. Grade 1 and 2 adverse events should only be recorded if considered clinically significant by the Investigator.

The Principal Investigator may delegate these duties to Sub-investigators and must ensure that these Sub-investigators are qualified to perform these duties under the supervision of the Principal Investigator and that they are listed on the FDA Form 1572.

9.8 SERIOUS ADVERSE EVENTS DEFINITIONS

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

- Results in death
- Is life-threatening

(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

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

Any death for any reason occurring within 30 days of the subject receiving study drug, regardless of the subject having discontinued from the study must be reported to the Janssen Scientific Affairs and Amgen Global Safety as an SAE.

HOSPITALIZATION

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

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

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]
- [For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.]

LIFE-THREATENING CONDITIONS

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

9.9 ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS (DARATUMUMAB)

All SAEs occurring from the time that the subject signs consent for study participation through 30 days after the last administered dose of study drug will be reported. All SAEs, regardless of relationship to study drug, must be followed to resolution or to stabilization if improvement or resolution is not expected.

If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report as well as the appropriate form for Study Discontinuation.

The PRINCIPAL INVESTIGATOR is responsible for notifying the appropriate Regulatory Agencies, when required, and in accordance with applicable laws and regulations of any Expedited Safety Reports. Generally, these are all SAEs that are judged to be unexpected and related to study drug(s), as specified in ICH E2B guidelines: Clinical Safety Data Management Data Elements for Transmission of Individual Case Safety Reports. However, certain Regulatory Agencies may have additional requirements for expedited safety report submissions.

This submission of IND Safety Reports (North America) or Suspected Unexpected Serious Adverse Reactions (SUSARS [Europe]) will be cross referenced according to local regulations to Janssen Investigational Compound Number (IND, CSA, etc) at the time of submission.

The Investigator is also responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), in accordance with local regulations, of all SAEs.

INDIVIDUAL CASE SAFETY REPORTS (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 J&J medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected J&J 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)
- J&J protocol ID

PRODUCT QUALITY COMPLAINT (PQC)

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

Examples of PQC include but not limited to:

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

SPECIAL REPORTING SITUATIONS (DARATUMUMAB)

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

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

- Any failure of expected pharmacological action (i.e., lack of effect) of a J&J medicinal product

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

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

PREGNANCY

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

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

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

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

All pregnancies are considered a SAE and will require expedite reporting. Investigators will follow the outcome of the pregnancy for (spontaneous abortion,(any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly.

MAINTENANCE OF SAFETY INFORMATION

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

9.9.6 PROCEDURES FOR REPORTING SAFETY DATA AND PRODUCT QUALITY COMPLAINTS (PQC) FOR JANSSEN MEDICINAL PRODUCTS TO JANSSEN SCIENTIF AFFAIRS, LLC

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

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

9.9.6.1 SAEs. Adverse Events of Special Interest and Special Reporting Situations

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

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

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

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

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

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

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

- Copies of any and all relevant extraordinary (not including routine intiaion or follow-up ICSR submission) correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to J&J using a transmission method in Section 9.9.8 from this protocol **within 24 hours of such report or correspondence being sent to applicable health authorities**.

9.9.6.2 Non-Serious AEs

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

9.9.6.3 PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected

pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

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

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

9.9.7 REPORTING PROCEDURES FOR REPORTING SAFETY DATA AND PRODUCT QUAKLITY COMPLAINTS (PQCS) FOR NON-JANSEN MEDICIAL PRODUCTS

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

9.9.8 TRANSMISSION METHODS

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

- Electronically via J&J SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
- Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

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

9.9.9 SAEs LISTING

At a minimum, on a semi-annual basis and at the end of the Study, Janssen Scientific Affairs, LLC will provide to the INSTITUTION and/or PRINCIPAL INVESTIGATOR, a listing of all SAEs reported to the COMPANY. SPONSOR and/or PRINCIPAL INVESTIGATOR will review this listing and will resolve any discrepancies with the data provided by the COMPANY.

9.9.10 DISSEMINATION OF SAFETY INFORMATION FROM J&J TO INSTITUTION/PRINCIPAL INVESTIGATOR

PRINCIPAL INVESTIGATOR will be responsible for submitting IND safety reports for the Study Product to INSTITUTION's IRB in accordance with Federal regulations 21 CFR 312.66. The PRINCIPAL INVESTIGATOR will provide a copy of each IND safety report to sub-investigators where the study design is either a multi-center or cooperative study.

COMPANY agrees to provide to the PRINCIPAL INVESTIGATOR IND safety reports for the J&J Medicinal Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred)..

9.9.11 CONTACTING JANSSEN SCIENTIFIC AFFAIRS, LLC REGARDING SAFETY

The names (and corresponding contact information) of the individuals who should be contacted regarding safety issues will be provided separately by J&J.

9.9.12 FINAL STUDY REPORT

The INSTITUTION/PRINCIPAL INVESTIGATOR will prepare a final report including a complete and full summary of all adverse events, special situations and pregnancy reports according to the timeframe outlined in the Research Funding Agreement

9.10 ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS (CARFILZOMIB)

All SAEs occurring from the time that the subject signs consent for study participation through 30 days after the last administered dose of study drug will be reported. All SAEs, regardless of relationship to study drug, must be followed to resolution or to stabilization if improvement or resolution is not expected.

If a subject is permanently withdrawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report as well as the appropriate form for Study Discontinuation.

The principal investigator, as an agent of the sponsor is responsible for notifying the appropriate Regulatory Agencies, when required, and in accordance with applicable laws and regulations of any Expedited Safety Reports. Generally, these are all SAEs that are judged to be unexpected and related to study drug(s), as specified in ICH E2B guidelines: Clinical Safety

Data Management Data Elements for Transmission of Individual Case Safety Reports. However, certain Regulatory Agencies may have additional requirements for expedited safety report submissions.

This submission of IND Safety Reports (North America) or Suspected Unexpected Serious Adverse Reactions (SUSARS [Europe]) will be cross referenced according to local regulations to Amgen Investigational Compound Number (IND, CSA, etc) at the time of submission.

The Investigator is also responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), in accordance with local regulations, of all SAEs.

Additionally, the Investigator is responsible for reporting adverse events to Amgen as described below:

The Investigator must inform Amgen Drug Safety in writing by Fax at the contact information listed below of all Expedited Safety Reports submitted to the relevant Regulatory Agencies. These notifications should be performed in parallel to the Regulatory Agency submissions [e.g., within 7 calendar days for any Fatal or Life-threatening SUSARs and within 15 calendar days for all other SUSARs], but in no case any later than 1 business day from the submission date. This must be documented on a FDA 3500A MEDWATCH form. This form must be completed and supplied to Amgen Drug Safety in English and accompanied by the global IST SAE Report Cover Page.

The initial report must be as complete as possible, at a minimum including the serious adverse event term(s), patient identifier, date of awareness of the event, an assessment of the causal relationship between the event and the investigational product(s), and name of the reporter (investigator). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up FDA 3500A MEDWATCH form and submitted to Amgen Drug Safety in the same timelines as outlined above. The Amgen ISS protocol number (Amgen ISS 20167173) and the institutional protocol number should be included on all reports to Amgen Drug Safety.

All other serious adverse events regardless of drug causality will be reported to Amgen on a FDA 3500A Medwatch form no later than 30 days from the time the sponsor-investigator becomes aware of the SAE. Amgen reserve the right to review the CRFs or source documents in response to any inquiries by regulatory agencies that the sponsor-investigator may receive.

Amgen Drug Safety and Pharmacovigilance Contact Information:

Phone: 1-888-814-8653
Drug Safety Fax: 1-805-480-9205

PREGNANCY

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

Females of childbearing potential should be advised to avoid becoming pregnant while being treated with carfilzomib. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus. Carfilzomib should only be used during pregnancy if the potential benefits to the mother outweigh the potential risks to the fetus. Carfilzomib can cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in subjects receiving the recommended doses. If carfilzomib is used during pregnancy , or if the subject becomes pregnant while taking carfilzomib, she should notifu the investigstor or study staff immediately.

Subjects, spouses, or partners will be followed through the outcome of the pregnancy. The Investigator will be required to notify Amgen of the pregnancy and discuss follow-up with the subject. It is not known if carfilzomib will reduce the efficacy of oral contraceptives. Due to an increased risk of venous thrombosis associated with carfilzomib, subjects currently using oral

contraceptives , or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of contraception.

All pregnancies are considered a SAE and will require expedite reporting. Investigators will follow the outcome of the pregnancy for (spontaneous abortion,(any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly .

Males of reproductive potential sho0uld be advised to avoid fathering a child while being treated with carfilzomib. The potential for carfilzomib to be transferred via semen and its effect on sperm is unknown. Male subjects treated with carfilzomib and/or their female partners (if of childbearing potential) should use effective contraceptive methods or abstain from sexual activity while treated with carfilzomib and for 90 days after treatment. Male subjects shou9ld refrain from donating sperm while on carfilzomib and for 90 days after treatment.
If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus.

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

No studies of carfilzomib have been conducted in breastfeeding women. Carfilzomib should not be used during breastfeeding. Breastfeeding women and women planning on breastfeeding may not participate in clinical trials with carfilzomib.

It is not known whether carfilzomib is present in human breast milk. Due to the potential for adverse effects in nursing infants from carfilzomib , a decision should be made whether to discontinue nursing or to discontinue carfilzomib, taking into account the potential benefit of carfilzomib to the mother. If a woman breastfeeds during the study, she must inform the investigator or study staff immediately. The investigator should notify Amgen that the subject has breastfed the infant and discuss the follow-up with the subject.

10 STATISTICAL CONSIDERATION

10.1 STUDY DESIGN

The study is a Single arm, multi-center, open label phase 2 trial with safety lead in and response-adapted therapy.

10.2 STUDY ENDPOINTS

10.2.1 PRIMARY ENDPOINTS

- Rate of MRD negative (10^{-5})remissions at completion of consolidation therapy

SECONDARY ENDPOINTS

- Toxicity profile of the KRdD combination.
- Rate of negative MRD at completion of induction.
- Rate of conversion from positive to negative MRD with auto-HCT.
- Rate of achievement of complete remission (CR) upon completion of induction and consolidation.
- Rate and kinetics of conversion from negative MRD to positive MRD upon treatment discontinuation.
- Progression-free survival (PFS) and overall survival (OS) for entire study population.

EXPLORATORY ENDPOINT

- PFS for patients with confirmed MRD(-) and undergoing observation without additional therapy.

10.3 SAMPLE SIZE CONSIDERATIONS

Due to limited data on the safety of the specific combination of agents being studied in the induction phase, a safety lead-in was performed and included 6 subjects. No dose limiting

toxicity was seen during the first 2 cycles in 2 or more subjects (in fact none of the first 6 subjects experienced dose limiting toxicity). The study was reviewed by the data safety monitoring board that recommended accrual will continue at the initial dose level.

The initial sample size considerations is based on Simon's optimal two-stage design (optimum design) to estimate the rate of MRD negative cases upon completion of consolidation and reduce the early futility of the study. A total of 67 evaluable patients will be enrolled that will achieve 80% power (and alpha=0.05) to test the primary hypothesis, i.e. at least 15% more MRD negative in the experimental intervention than in the benchmark, ~60 % MRD negative in the KRD- auto-HCT trial(45) and at least 75% MRD negative in the current protocol. Twenty-seven patients will be enrolled in the first stage; the trial will be terminated if 17 or fewer patients become MRD negative in the first stage. Based on the null hypothesis that P<=0.60 versus the alternative that P>=0.75, there is 69% probability of early termination if P=P0. If the trial goes on to the second stage, an additional 40 evaluable patients (total of 67 evaluable patients) will be studied. If the total number of subjects to become MRD negative is less than or equal to 46, the intervention will be considered futile. By accounting for ~20% of either patients drop out or subjects not informative for MRD, a total of 82 eligible patients will be required. The size of the study (n=67 informative subjects) will provide two-sided 95% confidence intervals for MRD negative estimate from 62.5% in lower limit to 84.4% in upper limit using Clopper-Pearson exact method for one proportion assuming the MRD negative rate is 75%

STATISTICAL CONSIDERATIONS FOR STUDY EXPANSION

As of August 2019 80 patients have been enrolled, 45 have reached end of induction therapy and 25 have reached end of consolidation 1. Seventy-seven of 80 patients (96%) are MRD evaluable (vs. ~80% originally estimated). Of the 23 patients who are MRD evaluable and are beyond consolidation 1, 18 (78%) have reached primary endpoint (vs. 75% originally estimated). The proportion of patients reaching primary endpoint is expected to increase as patients advance to consolidation 2 and 3. Therefore, with 18/23 patients already meeting primary endpoint, the study did not meet criteria for early termination during first stage of Simon's two stage design. (17 or fewer patients reaching primary endpoint among the first 27 evaluable).

Upon approval of protocol ammendment #4, the trial will be expanded to include a total of 123 patients (therefore 41 patients in addition to the 82 patients anticipated in original protocol and amendments 1, 2 and 3) in order to enable the exploratory objective. **Accrual will only continue if the study does not meet criteria for futility upon completion of Simon's second stage (i.e. 46 or fewer patients reach primary endpoint at completion of second stage among the first 67 MRD evaluable patients).**

The exploratory objective is to describe progression-free survival (PFS)of high-risk [HR; i.e. myeloma cells harboring del17p or t(4;14) or t(14;16)]and standard risk (SR) patients reaching confirmed MRD negative status (10^{-5}) and discontinuing therapy. High-risk patients account for a minority subset of patients with NDMM (currently at 27.5% in this study, 15-20% in most trials for NDMM) and are also less likely to achieve MRD negative status upon therapy. Therefore, in order to fulfill the exploratory objective of the study, some enrichment of the cohort for high-risk patients is necessary. In order to estimate the optimal accrual of HR and SR patients we assumed the rate of MRD evaluable patients to be 95% (consistent with current findings), the proportion of SR patients who achieve confirmed MRD negative status to be 85% and the proportion of HR patients who achieve confirmed MRD negative status to be 75%. Different scenarios utilizing these parameters are displayed in Table 11. The scenario with 65% patients evaluable for exploratory objective being SR and 35% being HR patients provides the best balance between HR enrichment and duration of enrollment. This scenario anticipates a total of 77 SR and 46 HR patients being accrued (Figure below) so effectively 37.4% of accrued patients being HR (46/123) to yield 62 SR and 33 HR patients with confirmed MRD negative status and evaluable for exploratory objective.

Table 11- Different scenarios of trial enrichment for HR patients.

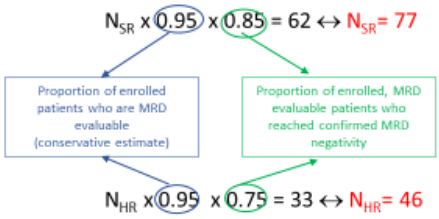
	Standard risk/High risk			
	70/30	65/35	60/40	50/50
N(SR) evaluable for exploratory objective	68	**62**	57	47
N(HR) evaluable for exploratory objective	29	**33**	38	47
Total N in exploratory analsysis	97	95	95	94
N(SR) to be accrued	84	**77**	71	58
N (HR) to be accrued	41	**46**	53	66
Accrual SR/month	5.6	5.6	5.6	5.6
Accrual HR/month	2.4	2.4	2.4	2.4
Current accrual SR	58	58	58	58
Current accrual HR	22	22	22	22
N of months to complete SR accrual	4.6	3.4	2.2	0.0
N of months to complete HR accrual	7.8	10.1	13.1	18.3
Total N to be accrued	124	123	124	124

Figure 1 – Sample size calculation for exploratory objective.

Exploratory objective: The describe progression-free survival (PFS)of high-risk (HR) and standard risk patients reaching confirmed MRD negative status (10^{-5}) and discontinuing therapy.

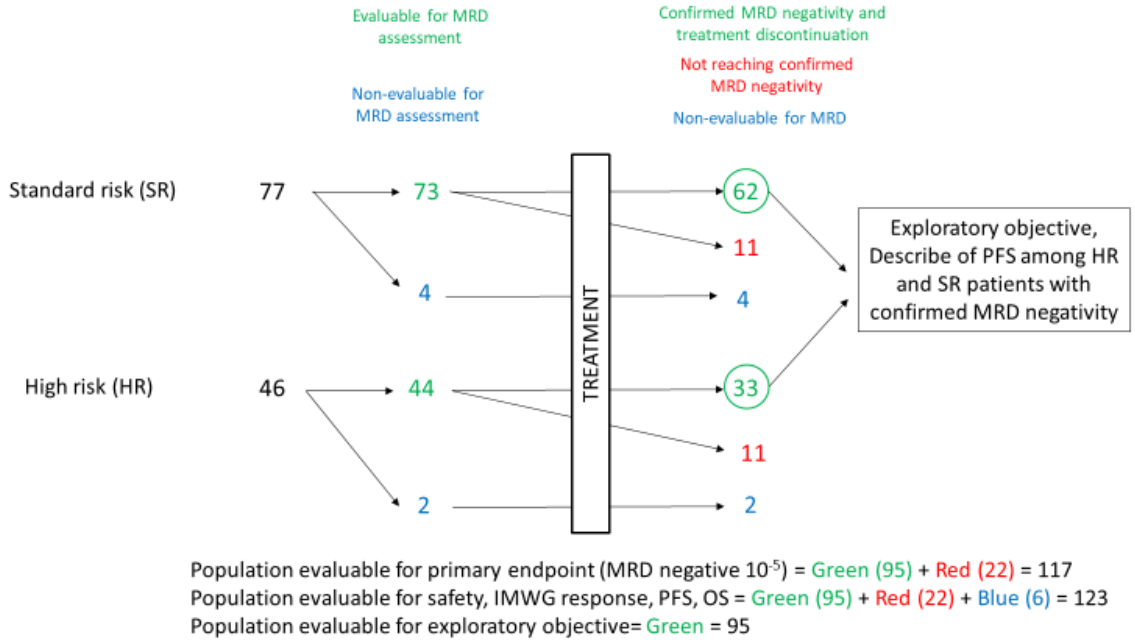
If 65% of patients reaching confirmed MRD negative status are SR and 35% are HR, a total of 95 patients (62 SR, 33 HR) are necessary.

The N to accrue from each risk category can be calculated as follows



Therefore new sample size = 123 patients, consisting of 77 SR plus 46 HR patients

Figure 2- Expected patient disposition



Upon activation of protocol ammendment #4 the UAB CTNMO will ensure that enrollment does not exceed 77 standard risk patients and 46 high risk patients. Once accrual target is reached for one of the risk categories (e.g SR) accrual will only continue in the other risk category.

Based on data from patients reaching MRD negativity followed by observation described from the IFM 2009 trial(21), we estimate the 2-year PFS (from discontinuation of therapy) of patients with confirmed MRD negativity to be ≥ 75% for both HR and SR patients. Table 12 provides confidence interval for a few different possibilities of 2-year PFS for HR and SR cohorts.

Table 12- Estimated 2-year PFS and 95% confidence interval for HR and SR patients.

	HR N=33			SR N=62		
Scenarios for 2-yr PFS (%)	75	85	95	75	85	95

2-sided 95% CI (%)	60.2-89.8	72.8-92.2	87.6-100.0	64.2-85.8	76.1-93.9	90.0-100.0

10.4 STATISTICAL ANALYSIS

GENERAL STATISTICAL ANALYSIS

Continuous endpoints will be summarized using descriptive statistics, which will include the number of patients with a valid measurement (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. The safety endpoints will be listed and/or summarized by relevant time points, as appropriate. In general, the baseline value for efficacy and safety variables is the last non-missing value before the first dose of study treatment. Data listings will be created to support each table and to present all data. Statistical analysis will be done with SAS v.10.3.

MISSING DATA HANDLING

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to pre specified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

ASSESSMENT OF SAFETY

All enrolled subjects who receive ≥ 1 dose of study drug will be included the safety analysis. Safety assessments will consist of monitoring and recording DLTs, AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other

laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent AEs will be reported by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Summaries will also be presented by the severity of the AE (per Common Terminology Criteria For Adverse Events [CTCAE],v4.03) and by relationship to study drug.

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments and physical exams will be tabulated and summarized.

Additional analyses will include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded and tabulated according to the World Health Organization Drug Dictionary (WHODRUG).

ANALYSIS OF EFFICACY PARAMETERS

The primary endpoint of MRD (-) rate will be estimated along with two-sided 95% CI using Clopper-Pearson exact method. The same method will be used to estimate rate of negative MRD at completion of induction; rate of conversion from positive to negative MRD with auto-HCT, rate of attainment of CR upon completion of consolidation and rate and kinetics of conversion from negative MRD to positive MRD upon treatment discontinuation.

Time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distribution, median time-to-event with 95% confidence interval, patients at

risk, patients with an event, patients censored and survival probabilities at selected time points. Progression-free survival (PFS) is defined as the interval from the start of therapy to the earlier of the following events: documentation of objective disease progression (appendix B), initiation of any non-protocol anti-myeloma therapy with exception of single agent lenalidomide in dose up to 15 mg/day (accepted maintenance therapy) or death from any cause. For the exploratory objective of describing PFS for patients with confirmed MRD negative status who discontinue therapy, PFS will be defined as the interval from discontinuation of therapy (and initiation of observation) until the earliest of the following events: documentation of objective disease progression (appendix B), initiation of any anti-myeloma therapy or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quartiles (including the median). Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of disease progression was objectively documented.

Overall survival (OS) is defined as the time from date of enrollment until date of death due to any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. Subjects who are completely lost to follow-up for survival will be censored at enrollment date. The analysis methods for overall survival will be similar to those described for progression free survival.

INTERIM AND SAFETY ANALYSIS

There will be continuous monitoring for safety. A sequential probability ratio test (SPRT) approach will be used (49). If there is strong evidence that the rate of grade 4 non-hematologic toxicities is 0.30 or above, as compared to a null rate of 0.15, the enrollment will be halt and a full DSMC review will be conducted. The stopping boundary is based on the likelihood ratio comparing the null rate of 0.30 versus the alternative rate of 0.15 using binomial likelihoods. If the ratio favoring a rate of 0.30 (vs. 0.15) ever exceeds 10, then the study will be stopped. A likelihood ratio of 10 is similar to a significance level of 0.05.

11 INVESTIGATIONAL PRODUCT

11.1 CARFILZOMIB DESCRIPTION

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

11.2 CARFILZOMIB FORMULATION

Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®).

11.3 CARFILZOMIB STORAGE

Lyophilized Carfilzomib for Injection must be stored at 2–8ºC under the conditions outlined in the separate Pharmacy Manual, in a securely locked area to which access is limited to appropriate study personnel.

11.4 CARFILZOMIB ACCOUNTABILITY

Amgen, Inc. and the Investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of UAB, Amgen and by regulatory authorities.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of UAB, Amgen and by regulatory authorities.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

This study uses an Amgen-supported Interactive Response Technology System (IRT) for study drug ordering. Training will be provided to investigators and their designees at the different sites at or prior to study initiation visit.

11.5 LENALIDOMIDE DESCRIPTION

Lenalidomide (revlimid ®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2Hisoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$ with molecular weight of 259.3 d.

11.6 LENALIDOMIDE FORMULATION

Lenalidomide is off-white to pale-yellow powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero. Lenalidomide will be utilized in this study as 5, 10, 15 and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

11.7 LENALIDOMIDE STORAGE

Lenalidomide will be stored by subjects according to manufacturer instruction reported on labels.

11.8 LENALIDOMIDE SUPPLIER

Lenalidomide is manufacted by Celgene ® and approved in the US for treatment of patients with multiple myeloma in combination with dexamethasone. The study will utilize commercial product acquired directly by the subject. Lenalidomide will not be distributed by study sites. Lenalidomide is only available upon patient registration in revlimid REMS®. Registration in and compliance with revlimid REMS® is required for subject enrolment and continuation on study.

.

11.9 DEXAMETHASONE DESCRIPTION

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally occurring chemicals produced by the adrenal glands. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs. The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11,17,21-trihydroxy-16Į-methylpregna-1,4-diene-3,20-dione. The empirical formula is $C_{22}H_{29}FO_5$

11.10 DEXAMETHASONE FORMULATION

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

11.11 DEXAMETHASONE STORAGE

Dexamethasone will be stored by subjects according to manufacturer instruction reported on labels.

11.12 DEXAMETHASONE SUPPLIER

The study utilizes commercially available dexamethasone and the drug will not be provided by the sponsor. Subjects will be responsible for self-administration of dexamethasone.

11.13 DARATUMUMAB DESCRIPTION

Daratumumab is a human IgG1 kappa monoclonal antibody directed at CD38, a transmembrane protein that is overly expressed on plasma cells and malignant myeloma cells, while having low expression on normal lymphoid, myeloid, as well as epithelial tissue. Functionally, daratumumab directly targets CD38-expressing tumor cells and promotes antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity and apoptosis.(33) Preclinical data has demonstrated robust antitumor activity in xenograft models, including those with lenalidomide and bortezomib resistant cell lines.

11.14 DARATUMUMAB FORMULATION

Daratumumab is a colorless to pale yellow, preservative-free solution available as 100mg/5ml (20 mg/ml) in a single-dose vial or 400 mg/20 ml (20 mg/ml) in a single-dose vial. Daratumumab is prepared using aseptic technique by mixing the appropriate dose in a sterile bag containing 0.9% sodium chloride injection, USP as indicated in table 2 .

11.15 DARATUMUMAB STORAGE

Daratumumab is stored in refrigeration at 2o.C to 8o.C. It must not be frozen or shaken and must be protected from light. Following dilution the infusion bag may be stored for up to 24h in a refrigerator at 2o.C to 8o.C protected from light.

11.16 DARATUMUMAB ACCOUNTABILITY

Janssen, Inc. and the Investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of UAB, Janssen and by regulatory authorities.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of UAB, Janssen and by regulatory authorities.

Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

11.17 MELPHALAN DESCRIPTION

Melphalan (L-phenylamine mustard, L-PAM, L-Sarcolysin) is an alkylating agent coupled to an amino acid. The molecular formula is $C_{13}H_{18}C_{12}N_2O_2$ and the molecular weight is 305.

11.18 MELPHALAN FORMULATION

Melphalan is commercially available and supplied as a sterile, freeze-dried powder. Each vial contains 50 mg melphalan hydrochloride and the inactive ingredient, povidone 20 mg. Reconstitute per manufacturer instructions using the diluent provided. Further dilution and administration may be done per institutional standards. The manufacturer recommends completion of administration of melphalan within 60 minutes of reconstitution.

11.19 MELPHALAN STORAGE

The intact packages of melphalan for intravenous administration should be stored at room temperature (15 - 30°C) protected from light. Shelf life surveillance of the intact dosage form is ongoing.

11.20 MELPHALAN SUPPLIER

Intravenous melphalan is commercially available for purchase by a third party. Its use in the clinical setting addressed by this protocol (high dose chemotherapy and autologous hematopoietic stem cell transplantation) is standard of care practice.

12 REGULATORY OBLIGATIONS

12.1 INFORMED CONSENT

The investigator will obtain written informed consent from all participating patients or their authorized representatives. Obtaining informed consent must be done according to International Conference on Harmonization- Good Clinical Practice Guidelines (ICH GCP). Copies of the signed document will be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

12.2 COMPLIANCE WITH LAWS AND REGULATIONS

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Amgen with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee reapproval throughout the duration of the study. Copies of the Investigator's annual report to the IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided to Amgen and Janssen, with copy to UAB CTNMO

Name: Pamela Dixon Hardwick
Address: 1802 6th Avenue South; NP 2515; Birmingham, AL 35294
Phone No: 205- 975-5387
Fax No: 205-975-9875
Email Address: pamdixon@uab.edu

The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected.

Amgen will provide study sites with any expedited safety reports generated from any ongoing studies with carfilzomib, changes to the Investigator's Brochure, and any other safety information which changes the risk/benefit profile of carfilzomib during the conduct of the study, to allow him/her to fulfill his/her obligation for timely reporting to the IRB/ECs and other Investigators participating in the study.

Upon completion of the trial, the Investigator must provide the IRB or Ethics Committee, Janssen and Amgen with a summary of the trial's outcome.

12.3 PRE-STUDY DOCUMENTATION REQUIREMENTS

Participating study sites cannot begin enrollment until an initiation letter has been issued from the UAB CTNMO. Each center is required to participate in an initiation conference call.

Before the start of this study and the shipment of study drug to a participating study site, the following documents must be on file at UAB CTNMO. Participating sites will be responsible for forwarding the initiation documents toUAB CTNMO.

All start-up documents can be submitted via electronic mail to pamdixon@uab.edu or via fax at (205) 975-9875. Please ensure that the fax cover page clearly identifies the site, study identifier and is addressed to ATTN: UAB CTNMO.

These documents are required to be submitted by each participating center:

1. U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator at the participating center.

2. The names of any sub-investigators at the participating center must appear on e 1572. Investigators must also complete all regulatory documentation as required by local regulations. This includes any required human subjects training required by the site's local IRB.

3. Current curricula vitae and documentation of professional licensure of the Principal Investigator and sub-investigators listed on the 1572.

4. Resumes and human subject protections documentation (e.g. NIH, CITI) for all research personnel (e.g. study coordinators, data managers and other research personnel) and documentation of ICH-GCP training.

5. A signed and dated investigator brochure acceptance form.

6. Written documentation of IRB approval of protocol (identified by title, protocol version and date of approval) for each site.

7. IRB approved study informed consent and HIPAA consent form. HIPAA consent language can be included within the study informed consent. Please note that all informed consent forms should be reviewed and approved by the UAB CTNMO prior to submission to the site's designated IRB.

8. A signed Confidentiality Agreement.

9. A signed Clinical Trial Agreement for each site.

10. Laboratory certifications (CAP, CLIAs) and laboratory reference value ranges for each laboratory listed on the site's 1572.

11. The UAB CTNMO site specific forms as specified in the investigator-initiated multicenter manual.

12.4 SUBJECT CONFIDENTIALITY

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by Amgen, its designee, the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB or Ethics Committee reviews, and FDA inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY COMPLETION

13.1.1 PROTOCOL AMENDMENTS

No modifications will be made to the protocol without the agreement of the sponsor-investigator. Changes that significantly affect the safety of the patients, the scope of the investigation, or the scientific quality of the study will require Institutional Review Board approval prior to implementation, except where the modification is necessary to eliminate apparent immediate hazard to human subjects. Any departures from the protocol must be fully documented in the protocol deviation case report form and the source documentation**.**

13.1.2 STUDY COMPLETION

The following data and materials are required by UAB CTNMO , Amgen and Janssen before a study can be considered complete or terminated:

1. Copies of protocol amendments and IRB approval/notification, if appropriate.
2. Copies of the IRB final report, documentation of submission to the IRB.
3. A summary of the study prepared by the Principal Investigator (Study report, manuscript and/or abstract).
4. All regulatory documents (e.g., updated curriculum vitae for each Principal Investigator, updated U.S. FDA Form 1572 for each site).

13.2 STUDY DOCUMENTATION AND ARCHIVE

13.2.1 DATA RECORDING

The Clinical Research Coordinator and Investigator will be responsible for the recording of all data on the electronic Case Report Forms (eCRFs) on OnCore system.

The Investigator will provide access to his/her original records to permit a representative from the funding or auditing institution(s) to verify the proper transcription of data. Data submission will be electronically via Fax or email.

13.2.2 RECORD RETENTION

Federal law requires that an Investigator maintain all study records for two years after the investigation is discontinued.

13.3 STUDY MONITORING AND DATA COLLECTION

13.3.1 MONITORING

UAB CTNMO will be responsible for the monitoring of study patient data and records. Monitoring will be performed centrally. All monitoring reports will be kept by the UAB CTNMO to ensure that all reports are contained in a central study file. The CTNMO manager or UAB internal auditor will be responsible for conducting the review of monitoring packets. A final monitoring report will be generated and issued to the site and will be kept in the central study file by the UAB CTNMO.

13.3.1.1 Frequency of Reviews

The each patient at each participating center will have their eligibility criteria reviewed prior to enrollment by the UAB CTNMO.

During the course of the study, each site will be selected for an audit by the UAB Quality Assurance Committee approximately once a year. Audit will include 10% of the subjects enrolled at the site. In addition to the once yearly QA audit, monitoring for each patient entered into this trial will be 100%. Sites are to send source information on each patient to the UAB CTNMO office where a shadow chart will be maintained on each subject for this trial. Source will be verified to data entered into the OnCore database.

13.3.2 PROTOCOL DEVIATIONS AND SAFETY REPORTING

A Protocol Deviation is any variance from the protocol involving a subject or subjects that is not approved by the IRB prior to its initiation or implementation, and occurs when a member of the study team departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval.

Any protocol deviation or serious adverse event will be reported by the subsite within 24 hours of notification. Protocol Deviations will be reported by completion of the hard copy Protocol Deviation Report form. Serious Adverse Events will be reported by completion of a MedWatch 3500A form and hard copy Serious Adverse Event form. For both Protocol Deviations and Serious Adverse Events, all required forms and any supporting clinical documentation should be submitted to the UAB CTNMO office within 10 days of notification.

13.3.3 DATA SAFETY MONITORING BOARD

The University of Alabama Comprehensive Cancer Center Data Safety Monitoring Board will have oversight of the protocol. The UAB CCC DSMB will meet at a minimum on a monthly basis to discuss hematology related trials.

In addition, all protocol deviations and SAEs as defined above will be reviewed by the UAB CCC DSMB for review during the DSMB monthly meetings. The coordinating center will review protocol deviation and SAE events for form completion and provide assistance in communicating to the subsite if more information is warranted. The UAB CTNMO will report the event report to the UAB CCC DSMB so that the information can be reviewed at the next available DSMB meeting. During the DSMB review, the DSMB can make recommendations for any further study action.

13.3.4 DATA COLLECTION

Data collection will be managed by the UAB CTNMO staff via the study database which is housed and maintained at UAB Cancer Center.

Time sensitive information such as patient registration, serious adverse events reporting, and protocol deviation reporting will be collected via completed hard copy form. These forms are available from the UAB CTNMO. . Information collected will be reviewed and processed by the UAB CTNMO.

The data will be initially reviewed for quality assurance purposes to identify any discrepancies or missing data. The staff of the UAB CTNMO will notify the participating site of

any data queries and manage the overall data quality of the study. If data received relates to a serious adverse event or protocol deviation, the information will be processed for report to the UAB CCC DSMB for review. The sponsor- investigator, Luciano Costa, MD and the assigned statistician, will also have access to study data for quality assurance and analysis purposes. During the course of the study, data quality will be monitored by random inspection of the completed forms by a designated monitor. Any problems detected will be discussed with the PI. If necessary, re-training of data collectors will be conducted.

All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed. The study will be subject to a yearly internal audit via the UAB CCC Quality Assurance Committee at a minimum and audits may occur more frequently at the request of the QA Committee.

14 REFERENCES

1. Ludwig H, Bolejack V, Crowley J, Blade J, Miguel JS, Kyle RA, et al. Survival and years of life lost in different age cohorts of patients with multiple myeloma. J Clin Oncol. 2010;28(9):1599-605.
2. Kyle RA, Rajkumar SV. Multiple myeloma. Blood. 2008;111(6):2962-72.
3. Cancer Facts & Figures 2016: American Cancer Society; 2016 [Available from: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf.
4. Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized controlled trial. Blood. 2008;112(8):3107-14.
5. Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H, et al. Phase III Study of the Value of Thalidomide Added to Melphalan Plus Prednisone in Elderly Patients With Newly Diagnosed Multiple Myeloma: The HOVON 49 Study. J Clin Oncol.
6. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348(19):1875-83.
7. Blade J, Rosinol L, Sureda A, Ribera JM, Diaz-Mediavilla J, Garcia-Larana J, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood. 2005;106(12):3755-9.
8. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996;335(2):91-7.
9. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349(26):2495-502.
10. Palumbo A, Cavallo F, Gay F, Di Raimondo F, Ben Yehuda D, Petrucci MT, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371(10):895-905.
11. Attal M, Lauwers-Cances V, Hulin C, Facon T, Caillot D, Escoffre M, et al. Autologous Transplantation for Multiple Myeloma in the Era of New Drugs: A Phase III Study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial). Blood. 2015;126(23):391-.
12. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906-17.
13. Durie B, Hoering A, Rajkumar SV, Abidi MH, Epstein J, Kahanic SP, et al. Bortezomib, Lenalidomide and Dexamethasone Vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial S…. Blood. 2015;126(23):25-.

14. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012;366(19):1759-69.
15. Palumbo A, Gay F, Cavallo F, Di Raimondo F, Larocca A, Hardan I, et al. Continuous Therapy Versus Fixed Duration of Therapy in Patients With Newly Diagnosed Multiple Myeloma. J Clin Oncol. 2015;33(30):3459-66.
16. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770-81.
17. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782-91.
18. Avet-Loiseau H, Corre J, Lauwers-Cances V, Chretien M-L, Robillard N, Leleu X, et al. Evaluation of Minimal Residual Disease (MRD) By Next Generation Sequencing (NGS) Is Highly Predictive of Progression Free Survival in the IFM/DFCI 2009 Trial. Blood. 2015;126(23):191-.
19. Korde N, Roschewski M, Zingone A, Kwok M, Manasanch EE, Bhutani M, et al. Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma. JAMA oncology. 2015;1(6):746-54.
20. Martinez-Lopez J, Lahuerta JJ, Pepin F, Gonzalez M, Barrio S, Ayala R, et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. Blood. 2014;123(20):3073-9.
21. Perrot A, Lauwers-Cances V, Corre J, Robillard N, Hulin C, Chretien ML, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. Blood. 2018;132(23):2456-64.
22. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. The Lancet Oncology. 2016;17(8):e328-46.
23. Paiva B, Gutierrez NC, Rosinol L, Vidriales MB, Montalban MA, Martinez-Lopez J, et al. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood. 2012;119(3):687-91.
24. Rawstron AC, Child JA, de Tute RM, Davies FE, Gregory WM, Bell SE, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. J Clin Oncol. 2013;31(20):2540-7.
25. Goicoechea I, Puig N, Cedena MT, Cordon L, Vidriales M-B, Burgos L, et al. Clinical Significance and Transcriptional Profiling of Persistent Minimal Residual Disease (MRD) in Multiple Myeloma (MM) Patients with Standard-Risk (SR) and High-Risk (HR) Cytogenetics. Blood. 2018;132(Suppl 1):112-.
26. Demo SD, Kirk CJ, Aujay MA, Buchholz TJ, Dajee M, Ho MN, et al. Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome. Cancer Res. 2007;67(13):6383-91.

27. Arastu-Kapur S, Shenk K, Parlati F, Bennett MK. Non-Proteasomal Targets of Proteasome Inhibitors Bortezomib and Carfilzomib. ASH Annual Meeting Abstracts. 2008;112(11):2657.
28. Vij R, Wang M, Kaufman JL, Lonial S, Jakubowiak AJ, Stewart AK, et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood. 2012;119(24):5661-70.
29. Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ, Lonial S, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012;120(14):2817-25.
30. Papadopoulos KP, Siegel DS, Vesole DH, Lee P, Rosen ST, Zojwalla N, et al. Phase I study of 30-minute infusion of carfilzomib as single agent or in combination with low-dose dexamethasone in patients with relapsed and/or refractory multiple myeloma. J Clin Oncol. 2015;33(7):732-9.
31. Lendvai N, Hilden P, Devlin S, Landau H, Hassoun H, Lesokhin AM, et al. A phase 2 single-center study of carfilzomib 56 mg/m2 with or without low-dose dexamethasone in relapsed multiple myeloma. Blood. 2014;124(6):899-906.
32. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hajek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. The Lancet Oncology. 2016;17(1):27-38.
33. Berenson JR, Cartmell A, Bessudo A, Lyons RM, Harb W, Tzachanis D, et al. CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. Blood. 2016;127(26):3360-8.
34. Dhedin N, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood. 2015;125(16):2486-96; quiz 586.
35. Niesvizky R, Martin TG, 3rd, Bensinger WI, Alsina M, Siegel DS, Kunkel LA, et al. Phase Ib dose-escalation study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2013;19(8):2248-56.
36. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Spicka I, Oriol A, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372(2):142-52.
37. Jakubowiak AJ, Dytfeld D, Griffith KA, Lebovic D, Vesole DH, Jagannath S, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood. 2012;120(9):1801-9.
38. Plesner T, Arkenau H-T, Gimsing P, Krejcik J, Lemech C, Minnema MC, et al. Daratumumab in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed or Relapsed and Refractory Multiple Myeloma: Updated Results of a Phase 1/2 Study (GEN503). Blood. 2015;126(23):507-.
39. de Weers M, Tai YT, van der Veer MS, Bakker JM, Vink T, Jacobs DC, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. J Immunol. 2011;186(3):1840-8.
40. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med. 2015;373(13):1207-19.

41. Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet. 2016.
42. Chari A, Lonial S, Suvannasankha A, Fay JW, Arnulf B, Ifthikharuddin JJ, et al. Open-Label, Multicenter, Phase 1b Study of Daratumumab in Combination with Pomalidomide and Dexamethasone in Patients with at Least 2 Lines of Prior Therapy and Relapsed or Relapsed and Refractory Multiple Myeloma. Blood. 2015;126(23):508-.
43. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(8):754-66.
44. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(14):1319-31.
45. Zimmerman T, Raje NS, Vij R, Reece D, Berdeja JG, Stephens LA, et al. Final Results of a Phase 2 Trial of Extended Treatment (tx) with Carfilzomib (CFZ), Lenalidomide (LEN), and Dexamethasone (KRd) Plus Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (NDMM). Blood. 2016;128(22):675-.
46. Jakubowiak AJ, Chari A, Lonial S, Weiss BM, Comenzo RL, Wu K, et al. Daratumumab (DARA) in combination with carfilzomib, lenalidomide, and dexamethasone (KRd) in patients (pts) with newly diagnosed multiple myeloma (MMY1001): An open-label, phase 1b study. Journal of Clinical Oncology. 2017;35(15_suppl):8000-.
47. Barr H, Dempsey J, Waller A, Huang Y, Williams N, Sharma N, et al. Ninety-Minute Daratumumab Infusion Is Safe in Multiple Myeloma. Blood. 2017;130(Suppl 1):1889-.
48. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22(2):414-23.
49. Li L, Kulldorff M. A conditional maximized sequential probability ratio test for pharmacovigilance. Statistics in medicine. 2010;29(2):284-95.

APPENDIX A: NCI-CTCAE VERSION 4.0

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) v4.0

Publish Date: June 14, 2010

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX B: RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Response category	Criteria
Stringent complete response (sCR)	• CR as defined below plus all of the following • Normal serum FLC ratio • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Complete response (CR)	• Negative immunofixation of the serum and urine • If only the measurable non-bone marrow parameter was FLC, normalization of FLC ratio • < 5% plasma cells in bone marrow • Disappearance of any soft tissue plasmacytomas.
Very good partial response (VGPR)	• PR as defined below plus all of the following: • Serum and urine M-component detectable by immunofixation but not on electrophoresis or • If at on study, serum measurable, ≥ 90% or greater reduction in serum M-component • Urine M-component <100 mg per 24 hour
Partial response (PR)	One of the following: • If serum and urine measurable, ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hour. • If only serum measurable (but urine not), a ≥ 50% reduction of serum M-protein. • If urine measurable (but serum not), a reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hour. • If only the measurable non-bone marrow parameter was FLC, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels or a 50% decrease in level of involved FLC with 50% decrease in ratio • If the bone marrow was only measurable parameter, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30% • In addition to the above criteria, if a plasmacytoma is present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.

Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR or PD
Progressive Disease (PD)	Increase of 25% from lowest response value in any of the following: • Serum M-component (absolute increase must be $\geq$ 0.5 g/dL), and/or • Urine M-component (absolute increase must be $\geq$ 200mg/24 h), and/or • Only in patients without measureable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10mg/dL) • Only in patients without measureable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the PC proliferative disorder

APPENDIX C: FOLLOW UP FORM

Submit this form electronically to ljcosta@uabmc.edu and pamdixon@uab.edu for patients in the follow up phase at least once a year (due 12 months from entering follow up phase or 12 months from last report) or every time there is progression, initiation of new anti-myeloma therapy, death or completion of MRD testing performed as part of routine care of the patient.

Subject identifier: __ __ __ - __ __

Date of submission: ___/___/___

Patient status at time of submission:

( ) Alive
( ) Dead. Date of death _____

Did patient experience IMWG-defined disease progression:

( ) No
( ) Yes. Date of progression _____

Did patient have any ClonoSEQ® MRD evaluation (performed as part of routine care of the patient) since entering follow up phase or since last form submitted

( ) No
( ) Yes. Please submit deidentified report to ljcosta@uabmc.edu and pamdixon@uab.edu

Patient current anti-MM therapy status

( ) None, on observation
( ) On lenalidomide maintenance, starting date _____
( ) On lenalidomide, initiated due to resurgence of MRD, starting date _____
( ) On another drug/combination, initiated due to resurgence of MRD
Starting date _____; Regimen _____
( ) On another drug/combination, initiated due to Progression
Starting date _____; Regimen _____
( ) Not applicable, patient deceased.