ID: UMCC 2018.056	Phase 2 Study With Minimal Residual Disease (MRD) Driven Adaptive Strategy in Treatment for Newly Diagnosed Multiple Myeloma (MM) With Upfront Daratumumab-based Therapy	NCT04140162

PROTOCOL UMCC 2018.056

Phase 2 study with Minimal Residual Disease (MRD) driven adaptive strategy in treatment for newly diagnosed multiple myeloma (MM) with upfront daratumumab-based therapy

IND Sponsor: Erica Campagnaro, MD
University of Michigan
C354 Med Inn
1500 E Medical Center Dr
Ann Arbor, MI 48109-5848
(734) 647-8902
ericacam@med.umich.edu

Biostatistician: Phil Boonstra
University of Michigan
(734) 615-1580
philb@med.umich.edu

National Scientific Lead: Jing Christine Ye, MD, MSc
MD Anderson Cancer Center
1515 Holcombe Blvd, Unit 429
Houston, TX 77030-4009
T: 713-794-3234
F: 713-563-5067
JCYe@mdanderson.org

Coordinating Center University of Michigan

Study Drug: Daratumumab, Darzalex

Initial version: 05/14/2018
Amended: 07/31/2018
10/15/2018
11/01/2018
12/17/2018
08/28/2019
03/24/2020
08/25/2020
09/02/2021
10/06/2022
01/23/2023

Study drug and funding support is provided by Janssen Scientific Affairs, LLC

NOTE: To effectively manage **restrictions** put in place during public health or civil emergency or restrictions **(**i.e. COVID-19 pandemic**)** changes to protocol-required items **are to be made** to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to infectious pathogens). These changes are listed in **Appendix F** of the protocol (**Contingency Operation Plan**)

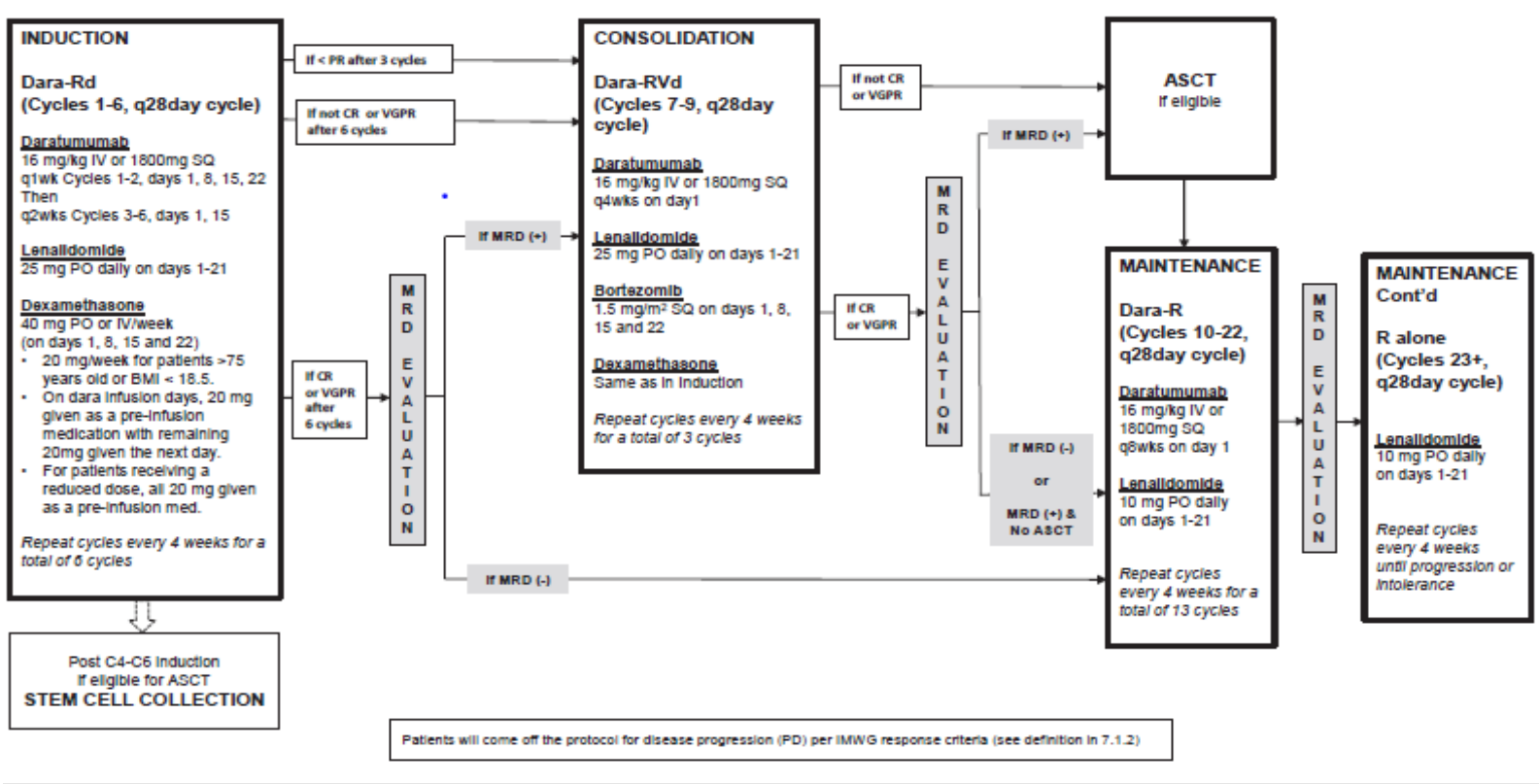
TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCT	Autologous stem cell transplant
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
AUClast	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
BSA	Body surface area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBCD	Complete Blood Count with Differential
Cmax	Maximal concentration
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRCL	Creatinine clearance
CRF	Case report form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
Dara-R	Study maintenance therapy consisting of daratumumab + lenalidomide
DaraRd	Study induction therapy consisting of daratumumab + lenalidomide + dexamethasone
DLT	Dose Limiting Toxicity
DOAC	Direct oral anticoagulant
DRVd	Study consolidation therapy consisting of daratumumab + lenalidomide + bortezomib + dexamethasone
DSMC	Data and Safety Monitoring Committee
DSMR	Data and Safety Monitoring Report
FCBP	Females of childbearing potential
FLC	Free light chain
GCP	Good clinical practices
H&P	History & Physical Exam
HRPP	Human Research Protections Program
HZV	Herpes zoster virus
ICF	Informed consent form
IDE	Investigational Device Exemption
IMWG	International Myeloma Working Group
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion Related Reactions

IV (or iv)	Intravenously
mAB	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells
MM	Multiple myeloma
MRD	Minimal Residual Disease
MSC	Multi-Site Coordinator
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NGF	Next-generation flow cytometry
NGS	Next-generation sequencing
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PI	Proteasome inhibitor
p.o.	per os/by mouth/orally
PQC	Product quality complaints
PR	Partial Response
PRC	Protocol Review Committee
QARC	Quality Assurance Review Committee
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SIFE	Serum immunofixation electrophoresis
SPEP	Serum protein electrophoresis
SOC	Standard of care
SPGT	Serum Glutamic Pyruvic Transaminase
SQ	Subcutaneous
SUV	Standardized uptake volume
TTP	Time to progression
UAP	Unanticipated Problem
ULN	Upper limit of normal
U-PEP	Urine M-protein
VGPR	Very good partial response
VTE	Venous thrombotic events
WBC	White Blood Cells

STUDY SCHEMA



STUDY SYNOPSIS

Title	Phase 2 study with minimal residual disease (MRD) driven adaptive strategy in treatment for newly diagnosed multiple myeloma (MM) with upfront daratumumab-based therapy
Phase	Phase II
Methodology	Single arm, uncontrolled, non-randomized
Study Duration	44 months until primary endpoint (MRD evaluation at the end of induction +/- consolidation) 60 months for the entire study until the end of maintenance therapy
Study Center(s)	Multi-center; 4 centers
Objectives	Primary Objective To determine the rate of MRD negativity after daratumumab-based induction and consolidation therapy if necessary, in both transplant eligible and ineligible newly diagnosed MM patients. Secondary Objectives 1. To describe the overall survival (OS) of patients who received daratumumab-based combination regimen. 2. To describe the progression free survival (PFS) of patients who received daratumumab-based combination regimen. 3. To describe the rate of MRD conversion after consolidation in patients who were MRD positive after initial induction. 4. To describe duration of sustained MRD negativity at time points of post-induction, post-consolidation, and post-1year maintenance. 5. To determine the quality of life of patients enrolled on the study as reflected in patient-reported outcomes. 6. To evaluate the safety and tolerability of daratumumab-based combination regimens in both transplant eligible and ineligible patient populations. 7. To estimate the proportion of patients with a successful stem cell mobilization after receiving daratumumab-based induction therapy. Exploratory Objectives 1. To correlate bone marrow MRD status with imaging MRD results 2. To correlate MRD status change with changes in immune phenotypes throughout treatment stages. 3. To describe MRD results and clinical outcome in patients with high-risk cytogenetic features (including del17p), focusing on persistent MRD status in the presence of baseline high-risk cytogenetics by FISH.
Number of Subjects	50 evaluable participants (up to 57 enrolled)
Inclusion Criteria	1. Participants ≥ 18 years of age or legal age of consent per local regulations (whichever is greater). 2. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the participant at any time without prejudice to future medical care. 3. ECOG status (Appendix A) of ≤ 2 and able to tolerate all applicable treatments per investigator's evaluation and standard institutional criteria.

4. Both transplant eligible and ineligible myeloma patients can be included in this study. If applicable, participant should be able to tolerate all treatments per investigator's evaluation, including high-dose chemotherapy and autologous stem cell transplant (ASCT) based on standard criteria at the institution where this treatment will be administered.
5. Participant must have a diagnosis of active MM according to International Myeloma Working Group (IMWG) diagnostic criteria, which require the following findings:

   Clonal bone marrow plasma cells ≥ 10% or biopsy proven bony or extramedullary plasmacytoma and any one or more of the following myeloma defining events (end organ damage that can be attributed to the underlying MM):
   - Hypercalcemia: serum calcium >1 mg/dL higher than the upper limit of normal or serum calcium >11 mg/dL
   - Renal insufficiency: serum creatinine >2 mg/dL or creatinine clearance (CRCL) < 40 mL/min
   - Anemia: hemoglobin ≥ 2g/dL below the lower limit of normal or hemoglobin < 10g/dL
   - Bone lesions: one or more osteolytic lesions on imaging studies
   - One or more of the following biomarkers of malignancy:
     - Clonal bone marrow plasma cells ≥ 60%
     - Involved: uninvolved serum free light chain (FLC) ratio ≥ 100
     - > 1 focal lesion on MRI or PET/CT studies
6. Participant must also have measurable disease as defined by at least one of the following:
   - Serum M protein ≥ 1g/dL (except patients with IgD or IgA myeloma). For patients with IgD or IgA myeloma, a serum M-protein ≥ 0.5 g/dl will suffice, or
   - Urinary (Bence-Jones protein) ≥200 mg per 24 hours, or
   - Serum involved FLC ≥10 mg/dL with an abnormal FLC ratio
7. Baseline bone marrow or tissue sample available for Clonality ID in ClonoSEQ
8. Participant must be registered in and must comply with all requirements of REMS™ program for lenalidomide.
9. Female participant who:
   - Is post-menopausal for at least one year prior to study enrollment, OR
   - Is surgically sterile, OR
   - If of childbearing potential, must have a negative urine or serum pregnancy test within 10-14 days prior to and again within 24 hours of starting lenalidomide. They must also be willing to use TWO effective forms of contraception simultaneously from the time of signing the study consent until 90 days following the administration of the last dose of lenalidomide and 7 months following the administration of the last dose of bortezomib, OR
   - Agree to practice complete abstinence if that is aligned with their lifestyle, which does not include periodic abstinence or withdrawal.
10. Male participant, even if surgically sterilized, must agree to one of the following:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the

	last dose of lenalidomide and 4 months following the administration of the last dose of bortezomib, OR • Agree to practice complete abstinence if that is aligned with their lifestyle, which does not include periodic abstinence or withdrawal.
Exclusion Criteria	1. Diagnoses of smoldering MM (SMM), monoclonal gammopathy of undetermined significance (MGUS), non-secretory MM, plasma cell leukemia, AL amyloidosis, Waldenstrom's. macroglobulinemia, POEMS syndrome. History of SMM and/or MGUS is not excluded. 2. Known disease involvement of the CNS. 3. History of prior hematopoietic stem cell transplant of any type. 4. Received more than one cycle of anti-myeloma therapy prior to enrollment. Up to one cycle of myeloma therapy is allowed. Concomitant treatment is allowed with low-dose corticosteroids and bisphosphonates. The dose of corticosteroids for myeloma treatment should not exceed the equivalent of 160 mg of dexamethasone over a two-week period before initiation of protocol. Prednisone up to but no more than 10 mg po daily or its equivalent is allowed, for symptom management and comorbid conditions. 5. Significant renal insufficiency, defined as creatinine clearance <30ml/min per Cockcroft-Gault formula. 6. Hepatic impairment, defined as bilirubin >1.5 x institutional upper limit of normal (ULN) or AST (SGOT), ALT (SGPT), or alkaline phosphatase > 3x institutional ULN. 7. Absolute neutrophil count (ANC) < 1000 cells/mm^3 within 7 days of enrollment. Growth factor may not be used to meet ANC eligibility criteria. 8. Hemoglobin (Hgb) < 8g/dL within 7 days of enrollment. 9. Platelet count < 75,000 cells/mm^3 within 7 days of enrollment. Transfusion may not be used to meet platelet eligibility criteria. 10. Any condition, including laboratory abnormalities, that in the opinion of the investigator places the subject at unacceptable risk if subject were to participate in the study. 11. Major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from complications of the surgery. 12. Clinically significant uncontrolled peripheral neuropathy, defined as symptoms limiting activities of daily living (basic ADLs). 13. Symptomatic uncontrolled cardiac disease including congestive heart failure with New York Heart Association class III-IV symptoms, arrhythmia, unstable angina or myocardial infarction within the past six months, or any other uncontrolled or severe cardiovascular condition. 14. Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. 15. Clinically uncontrolled asthma of any classification or known moderate or severe persistent asthma within the past two years (see asthma guidelines. https://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf). 16. Serious intercurrent illness including but not limited to clinically relevant cerebrovascular disease, uncontrolled diabetes mellitus, cirrhosis, pulmonary disease. 17. Active autoimmune process or other disease requiring systemic immunosuppressive, monoclonal antibody, small molecule, or

	radiation therapy. However local radiation for myeloma related symptomatic treatment is allowed. 18. Participant is: • Seropositive for HIV • Seropositive for Hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]) o Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. o Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR. • Seropositive for Hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy). 19. History of additional active malignancy in the past five years (not including squamous cell or basal cell carcinoma of the skin or in situ cervical cancer). However, malignancy treated with curative intent with <5% chance of disease relapse / recurrence in the next two years is allowed. 20. Known contraindication to study required medications (including steroids) or appropriate prophylactic medications (e.g., acyclovir, aspirin, warfarin or low-molecular weight heparin). 21. Women with a positive pregnancy test during the screening period prior to study initiation or who are lactating. 22. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial. 23. Any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given. 24. Participants using strong CYP3A4 inducers are excluded unless the inducer can be switched to an alternative agent while receiving Bortezomib (See Section 10.3 CYP3A4 inducers)

Study Product(s), Dose, Route, Regimen	**Induction regimen Dara-Rd** (all study subjects, 28 day cycles, cycles 1-6, i.e. weeks 1-24): Daratumumab IV 16 mg/kg actual body weight or SQ 1800mg • Cycles 1-2 (Weeks 1-8) IV or SQ 1800mg weekly, on days 1, 8, 15, 22 • Cycles 3-6 (Weeks 9-24) IV or SQ 1800mg every two weeks, on days 1, 15 Lenalidomide 25 mg PO once daily, on days 1-21 Dexamethasone 40 mg PO or IV weekly • A reduced dose of 20 mg weekly for patients >75 years or body mass index [BMI] of <18.5 or if patient cannot tolerate the higher dose) • On the day of Dara infusion: 20 mg of the dexamethasone dose given as a pre-infusion medication for Dara with remaining 20 mg given the next day. • For patients receiving a reduced dose, all 20 mg given as a pre-infusion med. **Consolidation regimen Dara-RVd** (in post-induction MRD+ population, 28 day cycles, cycles 7-9, i.e. weeks 25-36): Daratumumab 16 mg/kg actual body weight IV or SQ 1800mg every four weeks, on day 1 Lenalidomide given 25 mg PO once daily, on days 1-21 Bortezomib 1.5 mg/m^2 SQ on day 1, 8, 15 and 22 Dexamethasone 40 mg PO/week **Maintenance regimen Dara-R** (all study subjects, 28 day cycles, cycle 10-22, i.e. weeks 37-88): Daratumumab 16 mg/kg actual body weight IV or SQ 1800mg every eight weeks, on day 1 Lenalidomide 10 mg PO once daily, on days 1-21, weeks 37-88 **Maintenance regimen lenalidomide** (28 day cycles, Cycles 23+) Lenalidomide 10 mg PO once daily, on days 1-21, until progression or intolerance Sites will continue to use IV daratumumab to treat existing study patients until the IV daratumumab stock on site has been exhausted. The sites will then transition existing patient to SQ daratumumab. New patients will be started on SQ daratumumab.
Duration of Administration	See above section
Statistical Methodology	To establish evidence that the true proportion of patients who can achieve the primary endpoint, defined as MRD negativity after induction + consolidation (if MRD+ after induction), is at least 23%. We propose a two-stage design, with an interim futility analysis after the primary endpoint is available on the first 20 evaluable enrolled patients. We will proceed to a final analysis with all 50 evaluable patients if at least 2/20 (10%) of patients achieve MRD negativity after consolidation. If we proceed to the final analysis, then we will declare the trial outcome to be a success if at least 9/50 (18%) achieve MRD negativity. We consider a null scenario to be that in which the true proportion of patients achieving MRD negativity is no more than 10%. Based on simulations, we will declare success in a truly null scenario with probability less than 0.055 (one-sided type I error). We consider an interesting scenario to be that in which the true proportion is at least 23%. We will declare success in a truly interesting scenario with probability at least 0.83 (statistical power). We will also report confidence intervals for estimated proportions.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Multiple myeloma (MM) is an incurable malignancy caused by a clonal proliferation of plasma cells and is the second most common hematologic malignancy in the United States. Over the past two decades, symptomatic disease has been treated with combinations of novel therapies including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs) with or without corticosteroids and/or traditional chemotherapy. More recently the panel of novel agents has extended to monoclonal antibodies including anti-CD38, SLAMF7 as well as Histone Deacetylase inhibitor (HDACi). With the advent of these novel agents, improved treatment response has been associated with increased progression-free survival (PFS), overall survival (OS) and concomitant reduction in drug-related toxicity. Minimal Residual Disease (MRD) has been included in the NCCN guideline as new response criteria and a biomarker for deeper remission and is being considered by FDA as a surrogate marker for survival in clinical trials (Anderson 2016, Gormley, Farrell et al. 2016, Gormley, Turley et al. 2016, Harousseau and Avet-Loiseau 2017).

1.2 Study Agent(s) Background

Description:
Daratumumab, a CD38 antagonist, is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds CD38 expressed on the cell surface in a variety of hematological malignancies, including myeloma, lymphomas, and leukemias, as well as on other cell types and tissues with various expression levels. The antibody is produced in a recombinant mammalian cell line (Chinese Hamster Ovary [CHO]) using standard suspension cell cultivation and purification technologies, which include specific viral clearance procedures.

Nonclinical Pharmacology:
Daratumumab can induce complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and direct apoptosis after cross-linking, and can modulate CD38 enzymatic activity. In mouse xenograft models, daratumumab reduced tumor growth in both preventive and therapeutic settings. Daratumumab had no effect on proliferation of human peripheral blood mononuclear cells (PBMCs), and cytokine release was like other marketed therapeutic antibodies. Hence, daratumumab can recruit multiple effector mechanisms to facilitate the lysis of malignant cells in vitro and in vivo. In-vitro studies, using bone marrow mononuclear cells from patients with multiple myeloma, demonstrated increased killing of tumor cells when daratumumab was combined with lenalidomide, bortezomib, or both. Additionally, the upregulation of CD38 by pomalidomide or lenalidomide can enhance the activity of anti-CD38 antibodies including daratumumab. These observations suggest a strong potential for the treatment of CD38-expressing malignancies using daratumumab as monotherapy and in combinations (Lokhorst, Plesner et al. 2015, Lonial, Weiss et al. 2016).

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No carcinogenicity or genotoxicity studies have been conducted with daratumumab. No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development, or to determine potential effects on fertility in males or females.

Toxicology:
The potential toxicity of daratumumab was evaluated in a repeat dose study in chimpanzees. The primary toxicities identified in chimpanzees were infusion-related reactions during the first, but not subsequent, infusions and thrombocytopenia. The binding affinity of daratumumab is ≥15-fold higher for chimpanzee platelets than for human platelets, suggesting that thrombocytopenia may be less pronounced in humans. Depletion of specific lymphocyte phenotypic cell populations was observed in chimpanzees, which was expected based on the intended pharmacological effect of daratumumab. No

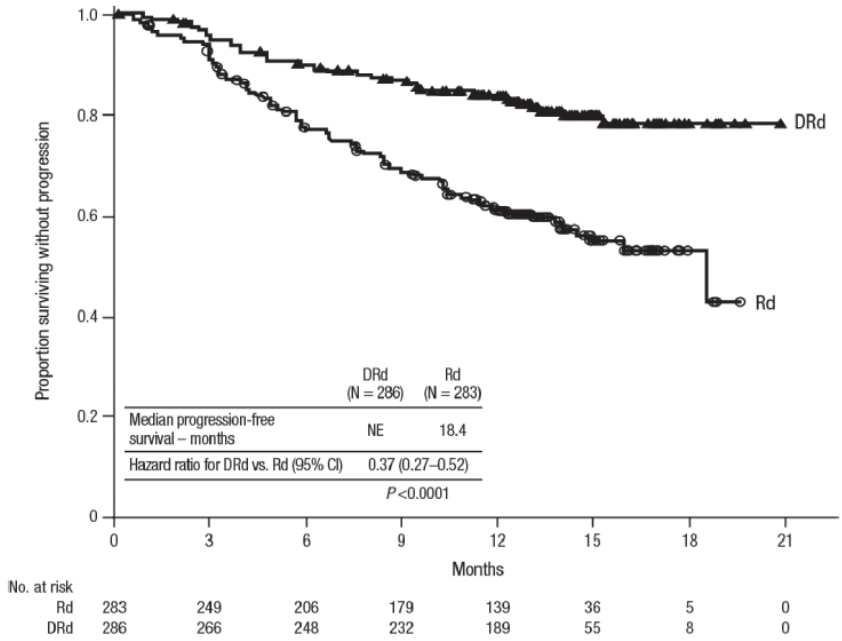
genotoxicity, chronic toxicity, carcinogenicity, or reproductive toxicity testing has been conducted. The local tolerability of the subcutaneous (SC) infusion of daratumumab in combination with recombinant human hyaluronidase (rHuPH20) was evaluated in rabbits. The combination was well tolerated and there were no daratumumab related macroscopic or microscopic findings.

Clinical Studies:
Combination Treatment with Lenalidomide and Dexamethasone POLLUX study, an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and lowdose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 65 years (range 34 to 89 years), 11% were ≥75 years, 59% were male; 69% Caucasian, 18% Asian, and 3% African American. Patients had received a median of 1 prior line of therapy. Sixty-three percent (63%) of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (86%) received a prior proteasome inhibitor (PI), 55% of patients had received a prior immunomodulatory agent, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and immunomodulatory agent. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib.

Efficacy was evaluated by progression-free survival (PFS) based on International Myeloma Working Group (IMWG) criteria. POLLUX study demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (hazard ratio [HR]=0.37; 95% CI: 0.27, 0.52; p<0.0001), representing a 63% reduction in the risk of disease progression or death in patients treated with DRd (Dimopoulos, Oriol et al. 2016, Plesner 2016).

Figure 1.2-1: Kaplan-Meier Curve of PFS in POLLUX Study



Additional efficacy results from POLLUX Study are presented in Table 1.2-1 below.

Table 1.2-1: Additional efficacy results from POLLUX Study[a]

	DRd (n=286)	Rd (n=283)
Overall response (sCR+CR+VGPR+PR)	261 (91.3%)	211 (74.6%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	51 (17.8%)	20 (7.1%)
Complete response (CR)	70 (24.5%)	33 (11.7%)
Very good partial response (VGPR)	92 (32.2%)	69 (24.4%)
Partial response (PR)	48 (16.8%)	89 (31.4%)

DRd = daratumumab-lenalidomide-dexamethasone;
Rd = lenalidomide-dexamethasone
a Based on Intent-to-treat population.
b p-value from Cochran Mantel-Haenszel Chi-Squared test.

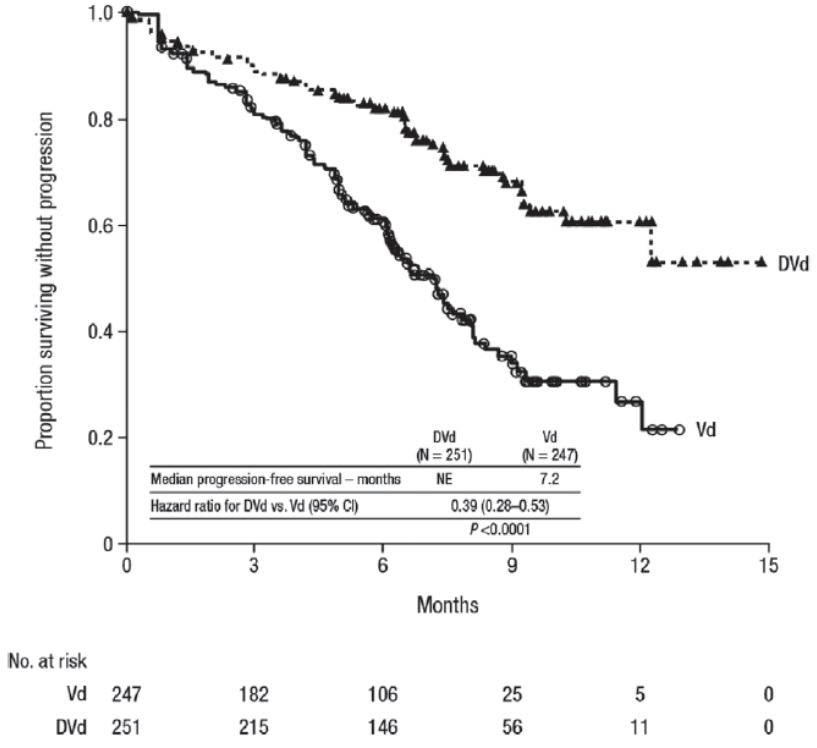
In responders, the median time to response was 1 month (range: 0.9 to 13 months) in the DRd group and 1.1 months (range: 0.9 to 10 months) in the Rd group. The median duration of response had not been reached in the DRd group (range: 1+ to 19.8+ months) and was 17.4 months (range: 1.4 to 18.5+ months) in the Rd group. With a median follow-up of 13.5 months, 75 deaths were observed; 30 in the DRd group and 45 in the Rd group.

Combination Treatment with Bortezomib and Dexamethasone CASTOR study, an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd). Bortezomib was administered by SC injection or IV infusion at a dose of 1.3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21-day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20

mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Bortezomib and dexamethasone were given for 8 three-week cycles in both treatment arms, whereas DARZALEX was given until disease progression. However, dexamethasone 20 mg was continued as a DARZALEX pre-infusion medication in the DVd arm. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information.

A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years); 12% were ≥75 years, 57% were male; 87% Caucasian, 5% Asian and 4% African American. Patients had received a median of 2 prior lines of therapy and 61% of patients had received prior autologous stem cell transplantation (ASCT). Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an immunomodulatory agent (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment and the proportions of patients refractory to any specific prior therapy were in general well balanced between the treatment groups. Thirty-three percent (33%) of patients were refractory to an immunomodulatory agent only, with 24% patients in the DVd arm and 33% of patients in the Vd arm respectively refractory to lenalidomide. Efficacy was evaluated by PFS based on International Myeloma Working Group (IMWG) criteria. CASTOR study demonstrated an improvement in PFS in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value < 0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd (Palumbo, Chanan-Khan et al. 2016).

Figure 1.2-2: Kaplan-Meier Curve of PFS in CASTOR Study



Additional efficacy results from CASTOR study are presented in Table 1.2-2 below.

Table 1.2-2: Additional efficacy results from CASTOR study[a]

	DVd (n=251)	Vd (n=247)
Overall response (sCR+CR+VGPR+PR)	199 (79.3%)	148 (59.9%)
P-value[b]	<0.0001	
Stringent complete response (sCR)	11 (4.4%)	5 (2.0%)
Complete response (CR)	35 (13.9%)	16 (6.5%)
Very good partial response (VGPR)	96 (38.2%)	47 (19.0%)
Partial response (PR)	57 (22.7%)	80 (32.4%)

DVd = daratumumab-bortezomib-dexamethasone;
Vd = bortezomib-dexamethasone
a Based on intent-to-treat population
b p-value from Cochran Mantel-Haenszel Chi-Squared test.

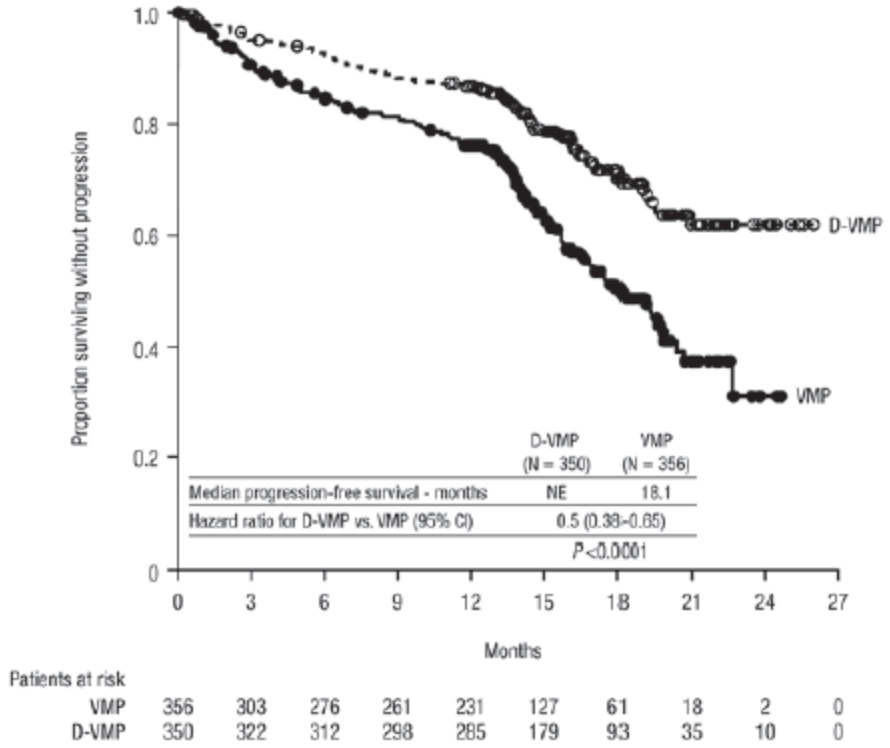
In responders, the median time to response was 0.8 months (range: 0.7 to 4 months) in the DVd group and 1.5 months (range: 0.7 to 5 months) in the Vd group. The median duration of response had not been reached in the DVd group (range: 1.4+ to 14.1+ months) and was 7.9 months (1.4+ to 12+ months) in the Vd group. With a median follow-up of 7.4 months, 65 deaths were observed,29 in the DVd group and 36 in the Vd group.

ALCYONE (NCT02195479), an open-label, randomized, active-controlled Phase 3 study, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed MM.Bortezomib was administered by subcutaneous (SC) injection at a dose of 1.3 mg/m^2 body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m^2, and prednisone at 60 mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX treatment was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomized: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients ≥75 years of age. The majority were white (85%) and, female (54%); 25% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 50% had an ECOG performance score of 1, and 25% had an ECOG performance score of 2. Nineteen percent of patients had ISS Stage I, 42% had ISS Stage II and 38% had ISS Stage III disease. Efficacy was evaluated by PFS based on IMWG criteria.

ALCYONE demonstrated an improvement in PFS in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months (95% CI:16.53, 19.91) in the VMP arm (hazard representing 50% reduction in the risk of disease progression or death in patients treated with D-VMP(Mateos, Dimopoulos et al. 2018).

Figure 1.2-3 Kaplan-Meier Curve of PFS in ALCYCONE



Additional efficacy results from ALCYONE are presented in Table 1.2-3 below.

Table 1.2-3: Additional efficacy results from ALCYONE

	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) n(%)[a]	318 (90.9%)	263 (73.9%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	63 (18.0%)	25 (7.0%)
Complete response (CR)	86 (24.6%)	62 (17.4%)
Very good partial response (VGPR)	100 (28.6%)	90 (25.3%)
Partial response (PR)	69 (19.7%)	86 (24.2%)
MRD negativity rate[a, c] n(%)	78 (22.3%)	22 (6.2%)
95% CI (%)	(18.0, 27.0)	(3.9, 9.2)
p-value[d]	<0.0001	
MRD negativity rate in patients with CR or better[c] n(%)	74 (49.7%)	22 (25.3%)
95% CI (%)	(41.4, 58.0)	(16.6, 35.7)

D-VMP = daratumumab-bortezomib-melphalan-prednisone;
VMP = bortezomib-melphalan-prednisone;
MRD = minimal residual

disease; CI = confidence interval
a Based on intent-to-treat population.
b p-value from Cochran Mantel-Haenszel Chi-Squared test.
c Based on threshold of 10-5.
d p-value from Fisher's exact test.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.5 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median duration of response had not been reached in the D-VMP group and was 21.3 months (range: 0.5+, 23.7+) in the VMP group.

Intravenous daratumumab for treatment of patients with multiple myeloma involves a lengthy infusion that affects quality of life, and infusion-related reactions are common. Subcutaneous daratumumab is considered to be easier to administer and to cause fewer administration-related reactions. In the COLUMBA study, SQ daratumumab was compared with IV daratumumab and data showed SQ daratumumab was non-inferior to intravenous daratumumab in terms of efficacy and pharmacokinetics and had an improved safety profile in patients with relapsed or refractory multiple myeloma (Mateos, Nahi et al. 2020). This led to the FDA approval of SQ daratumumab in May 2020 (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-daratumumab-and-hyaluronidase-fihj-multiple-myeloma).

Currently as the standard of care, IV daratumumab has been transitioned to SQ daratumumab in most of the institutions, including the participating institutions of this study. Patients on IV daratumumab have also been safely transitioned to SQ daratumumab. This transition reduces infusion reaction and infusion time for patients.

1.3 Other Agents

1.3.1 Lenalidomide

Lenalidomide (REVLIMID®) is an IMiD® compound, which has both immunomodulatory and anti-angiogenic properties that could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF (Dredge, Horsfall et al. 2005). In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production (Corral, Haslett et al. 1999). Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity (Schafer, Gandhi et al. 2003).

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis (Davies, Raje et al. 2001). In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1 growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patient's resistant to melphalan, doxorubicin and dexamethasone (Hideshima, Chauhan et al. 2000).

Indications
Lenalidomide is approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy. Lenalidomide is also indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. All other uses are considered investigational.

Clinical Experience

A Phase I study in participants with refractory or relapsed MM was conducted to identify the maximum tolerated dose (MTD) and to evaluate the safety of lenalidomide given orally for up to 4 weeks at 5 mg/day, 10 mg/day, 25 mg/day and 50 mg/day. Twenty-seven participants were enrolled, of whom 15 had undergone prior autologous stem cell transplantation and 16 had received prior thalidomide, with a median of 3 prior regimens (range 2-6). All participants had relapsed MM and 18 (72%) were refractory to salvage therapy. All participants at 50 mg/day demonstrated myelosuppression beyond day 28; thus this dose was considered to be the DLT. The 25 mg/day dose level as a continuous daily schedule of administration was considered MTD and has continued to be the recommended starting dose for MM treatment.

Data from two phase III trials comparing lenalidomide + dexamethasone to single agent dexamethasone in participants with relapsed and/or refractory MM were first presented at the 10th International Multiple Myeloma Workshop in Sydney Australia (Dimopoulos, Spencer et al. 2007, Weber, Chen et al. 2007). Participants who had received 1-3 prior therapies, and progressing on their last therapy were randomized to receive lenalidomide, 25 mg/d x 21 d, placebo d22-28 plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, q 28d or placebo daily x 28 d plus dexamethasone, 40 mg, d 1-4, 9-12, 17-20, q28d. Patients receiving the combination lenalidomide + dexamethasone demonstrated significantly higher overall response rates (ORR) than dexamethasone alone in both studies (61% vs 19.9% (Weber, Chen et al. 2007); 60.2% vs. 24%(Dimopoulos, Spencer et al. 2007); both $p<0.001$) (Dimopoulos, Spencer et al. 2007, Weber, Chen et al. 2007). Anemia, thrombocytopenia, neutropenia, fatigue, neuropathy, and constipation were also observed more often in the lenalidomide + dexamethasone group compared to the dexamethasone only group; however, these events were generally manageable.

1.3.2 Bortezomib

Bortezomib (VELCADE®) is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in nonclinical tumor models, including multiple myeloma. Furthermore, bortezomib-based treatment regimens have shown notable improvements in response, progression-free survival (PFS), and overall survival (OS) in comparison to non-bortezomib-based treatment for both transplant eligible and ineligible patients with newly diagnosed multiple myeloma.

Indications
Bortezomib is indicated for the treatment of patients with multiple myeloma. It is also indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Clinical experience
Please see Sections 1.2 and 1.4 for rationale regarding use in this study. Treatment with bortezomib has been associated with peripheral neuropathy, hypotension, cardiac toxicity (worsening of and development of cardiac failure), pulmonary toxicity (acute respiratory distress syndromes), posterior reversible encephalopathy syndrome, gastrointestinal toxicity (nausea, diarrhea, constipation, and vomiting), thrombocytopenia, neutropenia, tumor lysis syndrome, hepatic toxicity, and embryo-fetal risk. Commonly reported adverse reactions (incidence $\geq$ 20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, rash, lymphopenia, pyrexia, anorexia, Guillain-Barré syndrome, and demyelinating polyneuropathy.

1.3.3 Dexamethasone

Dexamethasone is a corticosteroid used in myeloma treatment for decades and is also considered to have synergistic effect when used in combination with other anti-myeloma agents. Its adverse reactions include hyperglycemia, increased appetite, weight gain, irritability, insomnia, impaired wound healing,

cataracts, and osteoporosis with long-term use. For further information regarding combination therapy, please refer to Sections 1.2 and 1.4.

1.4 Rationale

The concept of minimal residual disease (MRD) has been introduced to assess disease response in MM and represents a deeper remission compared with traditional best serological response i.e. complete response (CR). Two recent meta-analyses focusing on the association of MRD with survival outcome in MM showed MRD negativity is clearly associated with benefits of PFS and OS (Landgren and Giralt 2016, Munshi, Avet-Loiseau et al. 2016). MRD negative status is associated with longer overall OS, with favorable OS in MRD-negative patients overall compared with MRD-positive patients (HR, 0.57; 95%CI, 0.46-0.71; $P < .001$). Myeloma clinical practice guidelines (IMWG/NCCN) have incorporated MRD as the new response criteria since outcome advantage was clearly demonstrated in groups of patients who were MRD negative (Anderson 2016, Kumar, Paiva et al. 2016). The FDA has also agreed upon MRD as a potential regulatory end-point for clinical trials (Gormley, Farrell et al. 2016, Gormley, Turley et al. 2016).

While there is evidence demonstrating the association between MRD status and outcomes, there is a lack of research evaluating therapeutic options to reduce MRD burden in patients. In this phase 2 trial, we hypothesize that the combination of DaraRd as induction therapy, followed by DRVd consolidation therapy if needed, will result in the conversion of a true proportion of newly diagnosed myeloma to MRD-negative status, in both transplant eligible and non-eligible patients.

Daratumumab is a human IgG1 kappa monoclonal antibody, which binds to CD38-expressing cells and induces tumor cell death through multiple immune-mediated mechanisms. Because MM cells overexpress CD38, daratumumab was developed for its specificity and high affinity for this target. Furthermore, augmented cytotoxic T-cell expansion, activation and increased T-cell clonality have been seen after administration of daratumumab in patients with relapsed or refractory MM, suggesting a potential immunomodulatory role for this therapy.

Based upon published trial data DaraRd followed by DaraRVd in the frontline setting is proposed to achieve MRD conversion. The combination of daratumumab with both Rd and Vd has demonstrated impressive efficacy and comparable safety profile to RVd frontline regimen in standard of care. In the POLLUX trial, daratumumab with lenalidomide and dexamethasone (DaraRd) significantly prolonged PFS and reduced risk of disease progression or death compared to lenalidomide and dexamethasone (Rd) alone in patients with relapsed or refractory multiple myeloma (RRMM). Similar findings were shown in the CASTOR trial, which evaluated the combination of daratumumab with bortezomib and dexamethasone (DaraVd) in the relapsed/refractory setting compared with bortezomib and dexamethasone (Vd).

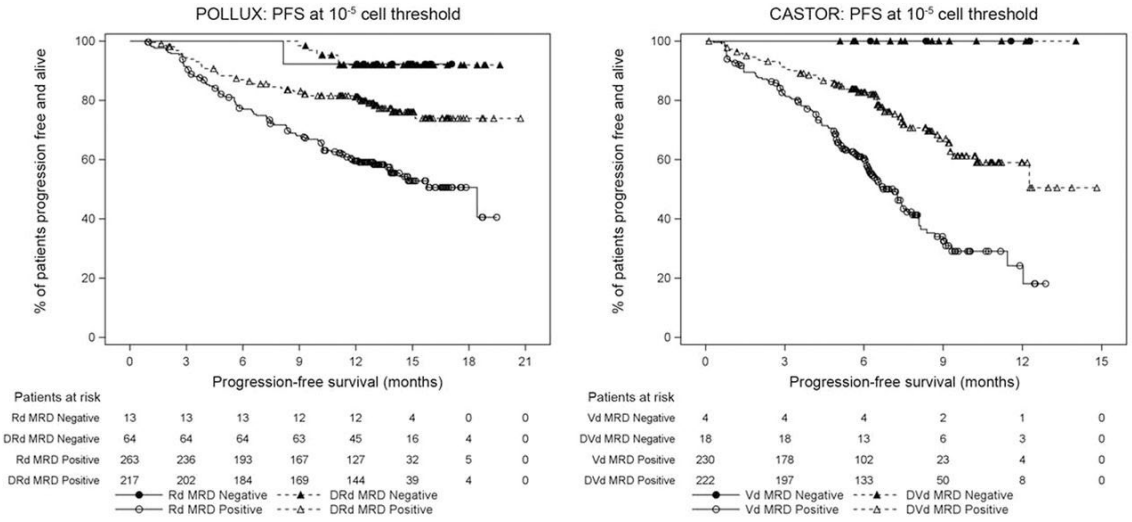
The addition of DARA to the standard of care regimens (Rd or Vd) not only resulted in significant improvements in PFS and ORR, but also drove deep clinical responses beyond CR. MRD was assessed in both POLLUX and CASTOR using next-generation sequencing (NGS) of B cell receptor (Ig). This is the first comprehensive and prospective study of MRD to date in randomized phase 3 clinical trials of RRMM patients and investigates the ability of daratumumab-containing regimens to drive deep responses in this challenging population. Median duration of follow-up was 13.5 months and 7.4 months in POLLUX and CASTOR, respectively. The addition of daratumumab to standard of care (SOC) regimens (Rd in POLLUX or Vd in CASTOR) resulted in significantly higher MRD negative rates at all three thresholds examined (10^{-4}, 10^{-5}, and 10^{-6}; Table 1.4-1). Additionally, patients who achieved MRD negative status experienced fewer PFS events compared with MRD positive patients at a threshold of 10-5 (Figure 1.4-1) (Dimopoulos, Oriol et al. 2016, Palumbo, Chanan-Khan et al. 2016).

These two studies demonstrate that daratumumab containing therapies can drive patients to remarkably deep levels of clinical response. Regardless of the SOC component, daratumumab-containing regimens (DaraRd and DaraVd) consistently demonstrated a ≥3-fold increase in the MRD-negative rate compared with the control groups (Rd and Vd) at all evaluated thresholds. Importantly, since patients who achieved MRD-negative status demonstrated low PFS event rates, the deep clinical responses induced by DARA may lead to improved survival (Avet-Loiseau, ASH abstract 2015).

Table 1.4-1

Sensitivity Threshold	POLLUX DRd vs Rd	CASTOR DVd vs Vd
10^{-4}	29.0% vs 7.8% OR (95% CI): 4.85 (2.93-8.03) *P*<0.000001	13.5% vs 2.8% OR (95% CI): 5.37 (2.33-12.37) *P*=0.000006
10^{-5}	22.4% vs 4.6% OR (95% CI): 5.99 (3.21-11.15) *P*<0.000001	7.2% vs 1.6% OR (95% CI): 4.69 (1.57-14.07) *P*=0.0017
10^{-6}	9.8% vs 2.1% OR (95% CI): 5.01 (2.04-12.30) *P*=0.000060	3.6% vs 0.8% OR (95% CI): 4.56 (0.97-21.30) *P*=0.028
OR, odds ratio.		

Figure 1.4-1



The encouraging outcome data from the Pollux and Castor studies in the relapsed setting of MM has prompted further studies in the frontline setting. Daratumumab is currently being studied in combination with RVd compared with RVd alone in newly diagnosed myeloma patients (Griffin study, NCT02874742). The combination of daratumumab, lenalidomide, and dexamethasone may represent a significant therapeutic advance for this patient population in this new era of MRD as a surrogate endpoint in clinical trials.

Bone marrow MRD detection by both flow cytometry and sequencing has been shown to correlate with clinical outcomes. Next Generation Flow Cytometry (NGF) and Next Generation Sequencing (NGS) have both been accepted for MRD detection with a sensitivity level higher than 10^{-5}. Patients achieving VGPR and above are considered the appropriate patient population for MRD detection per experts consensus (Landgren and Rustad 2019). NGF is widely acceptable in most institutions and NGS is only available in one commercial company. The University of Michigan is now part of the MRD Consortium within the International Myeloma Foundation, and NGF MRD detection is being implemented using EuroFlow standardization. We will determine MRD status at various stages of treatment in myeloma patients for treatment decision making per study schema. We plan to test MRD in patients achieved VGPR and above based on the experts consensus (Landgren and Rustad 2019).

It is unclear whether or not achieving MRD negativity will ameliorate the prognostic value of cytogenetics. One study suggested MRD monitoring is one of the most relevant prognostic factors in elderly myeloma patients, irrespectively of cytogenetic risk (Paiva, Cedena et al. 2016). Another study suggested that Dara-Rd in RRMM prolongs PFS and improves the depth of response regardless of

cytogenetic risk (Weisel, San Miguel et al. 2017). A more relevant question might be what is the significance of persistent MRD status in the presence of baseline high-risk cytogenetic features (Paiva, Gutierrez et al. 2012). Cautions were taken in with early switch to Velcade-containing consolidation if <=PR is achieved after 3 cycles of induction. Meanwhile, an exploratory objective is included for this patient population focusing on the persistent MRD in high-risk patients (see section 2.3).

2.0 STUDY OBJECTIVES

This is a prospective, single-arm trial evaluating the efficacy of an MRD-based decision-making strategy with upfront daratumumab-based therapy. We hypothesize that the true proportion of patients who can achieve MRD negativity after induction + consolidation (if still MRD+ after induction) is high, which we define as any response rate that is at least 23%.

2.1 Primary Objective

2.1.1 To determine the rate of MRD negativity after daratumumab-based induction and consolidation therapy if necessary in both transplant eligible and ineligible newly diagnosed MM patients.

2.2 Secondary Objectives To describe the overall survival (OS) of patients who received daratumumab-based combination regimen.

2.2.2 To describe the progression free survival (PFS) of patients who received daratumumab-based combination regimen.

2.2.3 To describe the rate of MRD conversion after consolidation in patients who were MRD positive after initial induction.

2.2.4 To describe duration of sustained MRD negativity at time points of post-induction, post-consolidation, and post-1year maintenance.

2.2.5 To determine the quality of life of patients enrolled on the study as reflected in patient reported outcomes.

2.2.6 To evaluate the safety and tolerability of daratumumab-based combination regimens in both transplant eligible and ineligible patient populations.

2.2.7 To estimate the proportion of patients with a successful stem cell mobilization after receiving daratumumab-based induction therapy.

2.3 Exploratory Objectives

2.3.1 To correlate bone marrow MRD status with imaging MRD results

2.3.2 To correlate MRD status change with changes in immune phenotypes throughout treatment stages

2.3.3 To describe MRD results and clinical outcome in patients with high risk cytogenetic features (including del17p), focusing on the persistent MRD status in the presence of baseline high risk cytogenetics by FISH**.**

2.4 Primary Endpoint MRD negativity either after induction or, if still MRD-positive after induction, after consolidation.

2.5 Secondary Endpoints Time from initiation of daratumumab-based combination regimen to death. Alive patients are censored at the last follow-up date.

2.5.2 Time from initiation of daratumumab-based combination regimen to death, or disease progression whichever comes first, where disease progression is according to the IMWG criteria. For subjects who have not progressed and are alive, data will be

censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

2.5.3 MRD negativity after consolidation in subjects who were MRD positive at the end of induction.

2.5.4 Time from first measured MRD negativity (post-induction) to loss of MRD negativity (post-consolidation and post-1-year maintenance) or last follow-up.

2.6 Exploratory Endpoints Imaging MRD result at time points of MRD evaluation.

2.6.2 Quantification and functional analysis of immune cell subsets from bone marrow samples and their changes at time points of MRD evaluation.

2.6.3 FACT/GOG-Neurotoxicity questionnaire and EQ-5 results at the frequency indicated in Table 6.2 (the first day of every cycle).

2.6.4 The occurrence of AEs as described in Section 8.

2.6.5 Successful stem cell mobilization after receiving 3 cycles of DaraRd induction.

2.6.6 MRD results and clinical outcome in patients with high risk cytogenetic features (including del17p).

3.0 PATIENT ELIGIBILITY

Participants must meet all the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a participant is enrolled. **No eligibility waivers will be granted for this clinical trial.**

3.1 Inclusion Criteria

3.1.1 Participants ≥ 18 years of age or of legal age of consent per local regulations (whichever is greater)

3.1.2 Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the participant at any time without prejudice to future medical care.

3.1.3 ECOG status (Appendix A) of ≤ 2 and able to tolerate all applicable treatments per investigator's evaluation and standard institutional criteria.

3.1.4 Both transplant-eligible and ineligible myeloma patients can be included in this study. If applicable, participant should be able to tolerate all treatments per investigator's evaluation, including high-dose chemotherapy and autologous stem cell transplant (ASCT) based on standard criteria at the institution where this treatment will be administered.

3.1.5 Participant must have a diagnosis of active MM according to International Myeloma Working Group (IMWG) diagnostic criteria, which require the following findings:

Clonal bone marrow plasma cells ≥10% or biopsy proven bony or extramedullary plasmacytoma and any one or more of the following myeloma defining events (end organ damage that can be attributed to the underlying multiple myeloma):

- Hypercalcemia: serum calcium >1mg/dL higher than the upper limit of normal or serum calcium >11mg/dL
- Renal insufficiency: serum creatinine >2 mg/dL or creatinine clearance <40mL/min
- Anemia: hemoglobin ≥ 2g/dL below the lower limit of normal or hemoglobin <10g/dL
- Bone lesions: one or more osteolytic lesions on imaging studies
- One or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cells ≥60%
  - Involved: uninvolved serum free light chain (FLC) ratio ≥100
  - >1 focal lesion on MRI or PET/CT studies

3.1.6 Participant must also have measurable disease as defined by at least one of the following:

- Serum M protein ≥1g/dL(except patients with IgD or IgA myeloma). For patients with IgD or IgA myeloma, a serum M-protein ≥ 0.5 g/dl will suffice, or
- Urinary Bence-Jones protein ≥200 mg per 24hours, or
- Serum involved FLC ≥10 mg/dL with an abnormal FLC ratio

3.1.7 Baseline bone marrow or tissue sample available for Clonality ID in ClonoSEQ

3.1.8 Participant must be registered in and must comply with all requirements of REMS program for lenalidomide.

3.1.9 Female participant who:

- Is post-menopausal for at least one year prior to study enrollment, OR
- Is surgically sterile, OR
- If of childbearing potential, must have a negative urine or serum pregnancy test with 10-14 days prior to and again within 24 hours of starting lenalidomide. They must also be willing to use TWO effective forms of contraception simultaneously from the time of signing the study consent until 90 days following the administration of the last dose of **lenalidomide and 7 months following the administration of the last dose of bortezomib**, OR
- Agree to practice complete abstinence if that is aligned with their lifestyle, which does not include periodic abstinence or withdrawal.

3.1.10 Male participant, even if surgically sterilized, must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days following the last dose of **lenalidomide and 4 months following the administration of the last dose of bortezomib**, OR
- Agree to practice complete abstinence if that is aligned with their lifestyle, which does not include periodic abstinence or withdrawal.

3.2 Exclusion Criteria

3.2.1 Diagnoses of smoldering MM (SMM), monoclonal gammopathy of undetermined significance (MGUS), non-secretory MM, plasma cell leukemia, AL amyloidosis,

Waldenstrom's macroglobulinemia, or POEMS syndrome. History of SMM and/or MGUS is not excluded.

3.2.2 Known disease involvement of the CNS.

3.2.3 History of prior hematopoietic stem cell transplant or organ transplant of any type.

3.2.4 Received more than one cycle of anti-myeloma therapy prior to enrollment. Up to one cycle of myeloma therapy is allowed. Concomitant treatment is allowed with low-dose corticosteroids and bisphosphonates. The dose of corticosteroids for myeloma treatment should not exceed the equivalent of 160 mg of dexamethasone over a two-week period before initiation of protocol. Prednisone up to but no more than 10 mg po daily or its equivalent is allowed for symptom management and comorbid conditions.

3.2.5 Significant renal insufficiency, defined as creatinine clearance <30ml/min per Cockcroft-Gault formula.

3.2.6 Hepatic impairment, defined as bilirubin >1.5 x institutional upper limit of normal (ULN) or AST (SGOT), ALT (SGPT), or alkaline phosphatase > 3x institutional ULN.

3.2.7 Growth factor may not be used to meet ANC eligibility criteria. Absolute neutrophil count (ANC) < 1000 cells/mm3 within 7 days of enrollment.

3.2.8 Hemoglobin (Hgb) < 8g/dL within 7 days of enrollment.

3.2.9 Platelet count < 75,000 cells/mm^3 within 7 days of enrollment. Transfusion may not be used to meet platelet eligibility criteria.

3.2.10 Any condition, including laboratory abnormalities that, in the opinion of the investigator, places the subject at unacceptable risk if subject were to participate in the study.

3.2.11 Major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from complications of the surgery.

3.2.12 Clinically significant uncontrolled peripheral neuropathy, defined as symptoms limiting activities of daily living (basic ADLs).

3.2.13 Symptomatic uncontrolled cardiac disease including congestive heart failure with New York Heart Association class III-IV symptoms, arrhythmia, unstable angina or

myocardial infarction within the past six months, or any other uncontrolled or severe cardiovascular condition.

3.2.14 Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal

3.2.15 Clinically uncontrolled asthma of any classification or known moderate or severe persistent asthma within the past two years (see asthma guidelines https://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf).

3.2.16 Serious intercurrent illness including but not limited to clinically relevant cerebrovascular disease, uncontrolled diabetes mellitus, cirrhosis, or pulmonary disease.

3.2.17 Active autoimmune process or other disease requiring systemic immunosuppressive, monoclonal antibody, small molecule, or radiation therapy. However, local radiation for myeloma related symptomatic treatment is allowed.

3.2.18 Participant is:

- Seropositive for HIV
- Seropositive for Hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg])
    - Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded.
    - Participants with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
- Seropositive for Hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

3.2.19 History of additional active malignancy in the past five years (not including squamous cell or basal cell carcinoma of the skin or in situ cervical cancer). However, malignancy treated with curative intent with <5% chance of disease relapse / recurrence in the next two years is allowed.

3.2.20 Known drug contraindication to study required medications (including steroids) or appropriate prophylactic medications (e.g., acyclovir, aspirin, warfarin or low molecular weight heparin).

3.2.21 Women with a positive pregnancy test during the screening period prior to study initiation or who are lactating.

3.2.22 Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

3.2.23 Any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given.

3.2.24 Participants using strong CYP3A4 inducers are excluded unless the inducer can be switched to an alternative agent while receiving Bortezomib (See Section 10.3 CYP3A4 inducers).

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Patient enrollment for this trial will be centrally managed by the Oncology Clinical Trials Support Unit (i.e. the Coordinating Center) of The University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log provided by the Coordinating Center.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient enrollment request to the Coordinating Center. After patient eligibility has been determined, a copy of the completed Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

A Multi-Site Coordinator of the Coordinating Center, who acts as the registrar, will review the submitted documents and process the enrollment. Sites should inform the Multi-Site Coordinator of a potential enrollment by 5 p.m. on the day prior to enrollment. Same day enrollments cannot be guaranteed.

The registrar will send an email to the requesting site registrar to confirm patient enrollment and randomization and to provide the study identification number and randomization number assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the registrar will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will have a screen fail number assigned to them, and will not receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Sites will continue to use IV daratumumab to treat existing study patients until the IV daratumumab stock on site has been exhausted. The sites will then transition existing patient to SQ daratumumab. New patients will be started on SQ daratumumab.

5.1.1 Induction Dara-Rd dosing schedule (in all subjects, 28-day cycles, cycles 1-6, i.e., weeks 1-24)

Daratumumab IV 16 mg/kg actual body weight or 1800mg SQ

- Cycles 1-2 (Weeks 1-8): IV or SQ 1800 mg weekly, on days 1, 8, 15, 22 (a total of 8 doses)
- Cycles 3-6 (Weeks 9-24): IV or SQ 1800 mg every two weeks, on days 1, 15 (a total of 8 doses, first dose of every two weeks dosing schedule is given at week 9)

Lenalidomide

- CrCl > 60 mL/minute: 25 mg PO once daily, on days 1-21 of repeated 28-day (4-week) cycles.
- CrCl 30 to 60 mL/minute: 10 mg once daily (may increase to 15 mg once daily after 2 cycles if tolerating treatment)

Dexamethasone 40 mg PO or IV weekly

- a reduced dose of 20 mg weekly for patients >75 years or body mass index [BMI] of <18.5 or if patient cannot tolerate the higher dose

- On the day of Dara infusion: 20 mg of the dexamethasone dose given as a pre-infusion medication for Dara with remaining 20 mg given the next day.
- For patients receiving a reduced dose, all 20 mg given as a pre-infusion med.

After 3 cycles of Induction Dara-Rd, if the subject's response is less than partial response (PR), the subject should move onto Consolidation Dara-RVd. If at least PR, continue with 3 additional cycles of Dara-Rd.

After 6 cycles of Induction Dara-Rd, if the subject's response is not achieving complete response (CR) or very good partial response (VGPR), the subject should move onto Consolidation Dara-RVd.

After 6 cycles of Induction Dara-Rd, if the subject's response is achieving CR or VGPR, proceed to MRD detection. If MRD is positive, move onto Consolidation Dara-RVd. If MRD is negative, move onto Maintenance Dara-R therapy.

Stem cell collection if eligible for ASCT, after 4 to 6 cycles of Induction Dara-Rd.

5.1.2 Consolidation Dara-RVd dosing schedule (in post-induction MRD+ subjects, 28-day cycles, cycles 7-9, i.e., weeks 25-36)

Daratumumab 16 mg/kg actual body weight IV or 1800mg SQ every four weeks, on day 1 (first dose of every-4-week dosing schedule is given at week 25).

Lenalidomide
- CrCl > 60 mL/minute: 25 mg PO once daily, on days 1-21 of repeated 28-day (4-week) cycles.
- CrCl 30 to 60 mL/minute: 10 mg once daily (may increase to 15 mg once daily after 2 cycles if tolerating treatment).

Bortezomib 1.5 mg/m^2 SQ on days 1, 8, 15 and 22.

Dexamethasone 40 mg PO or IV weekly.
- a reduced dose of 20 mg weekly for patients >75 years or BMI of <18.5 or if patient cannot tolerate the higher dose.
- On the day of Dara infusion: 20 mg of the dexamethasone dose given as a pre-infusion medication for Dara with remaining 20 mg given the next day.
- For patients receiving a reduced dose, all 20 mg given as a pre-infusion med.

After Consolidation Dara-RVd, if the subject has refractory disease, the subject should come off treatment for consideration of alternative treatment options.

After Consolidation Dara-RVd, if the subject's response is not achieving CR or VGPR, the subject should move onto ASCT if eligible.

After Consolidation Dara-RVd, if the subject's response is achieving CR or VGPR, the subject should proceed to MRD detection. If MRD is positive, the subject should move onto ASCT if eligible. If MRD is negative, the subject should move on to Maintenance Dara-R therapy.

After ASCT, subject should start Maintenance Dara-R therapy per institutional practice (usually around day+100 post-ASCT).

5.1.3 Maintenance Dara-R dosing schedule (in all subjects, 28-day cycles, cycles 10-22, i.e., weeks 37-88)

Daratumumab 16 mg/kg actual body weight IV or 1800mg SQ every eight weeks, on day 1 (first dose of every-8-week dosing schedule is given at week 37).

Lenalidomide 10 mg PO once daily, on days 1-21 of repeated 28-day (4-week) cycles, weeks 37-88.

- CrCl >60 mL/minute: 10 mg PO once daily. No dosage adjustment necessary.
- CrCl 30 to 60 mL/minute: 5 mg once daily

Repeat MRD detection after 13 cycles of Maintenance Dara-R therapy and then move to Maintenance Lenalidomide as below.

5.1.4 Maintenance Lenalidomide dosing schedule post Cycle 22

Lenalidomide 10 mg PO once daily, on days 1-21 of repeated 28-day (4-week) cycles, until progression or intolerance.

- CrCl >60 mL/minute: 10 mg PO once daily. No dosage adjustment necessary.
- CrCl 30 to 60 mL/minute: 5 mg once daily

5.1.5 Response Criteria per international myeloma working group consensus

See section 7.1.2

5.1.6 Missed Daratumumab Doses

If a planned dose of daratumumab is missed, administer the dose as soon as possible within 21 days and adjust the dosing schedule accordingly. If the delay is more than 21 days, contact the Sponsor-Investigator for further guidance.

5.1.7 IV Dara Infusion Administration

Administer daratumumab infusion intravenously at the infusion rate described below in Table 5.1-2. Consider incremental escalation of the infusion rate only in the absence of infusion reactions. For institutions using daratumumab rapid infusion protocol (Barr, Dempsey et al. 2018) as their standard of care, rapid infusions may be considered for Cycle 1 Day 15 and subsequent infusions ONLY for patients who tolerate Cycle 1 Day 8 without any grade (≥ grade 1) 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).

- Rapid infusion will be given in a total volume of 500 mL
- This allows for a rate of 200 mL/hr for the first 30 minutes and a rate of 400 mL/hr for the final 60 minutes.
- 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.

Table 5.1-2: Infusion rates for daratumumab administration

	Dilution volume	Initial rate (first hour)	Rate increment [a]	Maximum rate
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion [b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions [c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Consider incremental escalation of the infusion rate only in the absence of infusion reactions.
[b] Use a dilution volume of 500 mL only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.
[c] Use a modified initial rate for subsequent infusions (i.e., third infusion onwards) only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions. Otherwise, continue to use instructions for the second infusion.

For infusion reactions of any grade/severity, immediately interrupt the daratumumab infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of daratumumab as below:

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (Table 5.1-2).
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in Table 5.1-2. Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life threatening): Permanently discontinue daratumumab treatment.

Infusion-related reactions (IRRs) seen with daratumumab are generally mild, and commonly include nasal congestion, throat irritation, cough, dyspnea, chills and vomiting (Costello 2017). The highest risk of reaction is during the first or second exposure to daratumumab, with the risk declining with subsequent infusions. IRRs were seen in 42–71% of patients, and occurred most commonly during the first infusion. IRRs were grade 1/2 in almost all cases, none were grade 4, and discontinuations due to IRRs were rare (Lokhorst, Plesner et al. 2015, Costello 2017). The infusion rate can influence the occurrence of IRRs and should be followed according to Table 5.1-2. Premedications given 1 h prior to daratumumab as described in 5.8.8 can prevent IRRs.

If IRRs occur despite the premedication regimen, infusion should be paused immediately, even if only mild symptoms are detectable. The infusion should be held until the management as per local institutional practice guidelines is initiated and symptoms have resolved. Daratumumab can be restarted at a lower infusion rate following the resolution of symptoms (Laubach, Garderet et al. 2016) (Table 5.1-2). Oral corticosteroids on the first and second days following daratumumab infusions (as described in 5.1.8) can help to prevent the occurrence of delayed IRRs. Any patient with a history of obstructive pulmonary disease should be considered for short- and long-term bronchodilators and inhaled corticosteroids.

5.1.8 SQ Dara Injection Administration

Daratumumab (1800 mg) will be administered as SQ injection by manual push over approximately 3 – 5 minutes in the abdominal subcutaneous tissues in the left/right locations, alternating between individual doses. The current version of package insert has additional language that states the approximate location of injection around the naval: “inject

15mL of DARZALEX FASPRO into the subcutaneous tissue of the abdomen approximately 3 inches [7.5 cm] to the right or left of the navel over approximately 3-5 minutes."

- Never inject DARZALEX FASPRO into areas where the skin is red, bruised, tender, hard or areas where there are scars.
- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by pausing or slowing down delivery rate, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- During treatment with DARZALEX FASPRO, do not administer other medications for subcutaneous use as the same site as DARZALEX FASPRO.

The volume of the SQ solution will be 15 mL for the 1800 mg dose. Reasons for continued observation on subsequent daratumumab injection may include but are not limited to the following: subjects with a higher risk of respiratory complications (e.g., subjects with mild asthma or subjects with COPD who have an FEV1 < 80% at screening or developed FEV1 < 80% during the study without any medical history), subjects with infusion/injection related reactions (IRR) with the first injection of study drug, subject with decreased condition on day of dosing compared to prior dosing day. The dose of daratumumab will remain constant throughout the study. "Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX." As such our standard of care order is to monitor patient for 4 hours post administration of the first dose.

Table 5.1-3 Recommendations for the management of IRRs (adapted from Costello 2017).

IRR	**Action**
Grade 1 or 2	The infusion should be paused. When the patient's condition is stable, the infusion may be restarted at the investigator's discretion. Restart infusion rate at half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.
Grade 2 or higher event of laryngeal edema Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 h from onset	Patient must be withdrawn from treatment.
Grade 3 or higher	Infusion must be stopped, and the patient must be observed carefully until resolution of the IRR.
If the intensity of the IRR remains at grade 3 after 2 h	Patient must be withdrawn from treatment.
If the intensity of the IRR decreases to grade 1 or 2 within 2 h	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 intensity of the IRR returns to grade 3 after restart of the infusion	The procedure described above may be repeated at the investigator's discretion.
If the intensity of the IRR increases to grade 3 for a third time	Patient must be withdrawn from treatment 1. Permanently discontinue DARZALEX upon the third occurrence of a Grade 3 or greater infusion reaction. 2. Grade 4 (life threatening): Permanently discontinue DARZALEX treatment.
Grade 4	Permanently discontinue DARZALEX treatment.

5.1.8.1 SQ Injection

IRRs are systemic reactions related to daratumumab administration. Participants should be observed carefully during daratumumab administrations. Trained study staff at the

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

Infusion-related Reactions Grade 1 or Grade 2:
If the investigator assesses a Grade 1-2 IRR to be related to administration of study intervention, then the daratumumab SQ administration should be interrupted. When the participant's condition is stable, daratumumab SQ administration may be restarted at the investigator's discretion. Refer to the USPI for further details regarding continuation of daratumumab SQ administration.
If the participant experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the participant must be permanently discontinued from daratumumab SQ treatment.

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

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

5.1.9 Injection Site Reactions (ISR):

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

5.1.10 The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. Intravenous fluids (IVF) should be given to prevent volume depletion.
- Growth factors (e.g., granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted but should be used with caution after assessing benefit//risk. Their use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines; however, screening hemoglobin and platelet count must be independent of RBC and platelet transfusions per eligibility criteria.
- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.
- Radiation therapy to a localized mass is acceptable with prior approval of the Sponsor-Investigator.
- Prophylactic proton pump inhibitor or an H2 antagonist are recommended but NOT required and considered optional medications.
- Fluid deficit should be corrected before initiation of treatment and during treatment.
- Aspirin for venous thrombotic events (VTE) prophylaxis.
  Note: If a subject is allergic to aspirin, low-molecular-weight heparin or DOACs may be used. In subjects with a prior history of venous thrombosis, low-molecular-weight heparin or therapeutic doses of warfarin (target international normalized ratio [INR] 2-3) or DOACs are required (or follow most current guidelines for deep vein thrombosis [DVT] prophylaxis).
- Acyclovir 400 mg orally twice a day for herpes zoster virus (HZV) prophylaxis (or equivalent per institutional guidelines)

5.1.11 Pre-Infusion/Pre-Injection Medication for Dara-Rd, and Dara-RVd, and Dara-R

Administer the following pre-infusion/pre-injection medications to reduce the risk of infusion/injection reactions to all patients 1-3 hours prior to every infusion/injection of daratumumab:

- Corticosteroid (long-acting or intermediate-acting) combination therapy: Administer oral or IV 20 mg dexamethasone (or equivalent) prior to every daratumumab infusion/injection (and the remaining 20 mg on the day after the infusion). When dexamethasone is the background regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on Dara infusion days.
- Oral montelukast 10 mg prior to dose of Dara, for doses 1-4
- Antipyretics (oral or intravenous acetaminophen 650 to 1000 mg per daratumumab prescribing information)
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg; and oral or intravenous famotidine 20 mg if used per institutional guideline). Avoid IV use of promethazine.
- If the subject does not experience IRR after the first 8 doses, pre-infusion/pre-injection medications can be discontinued per institutional practice.

5.1.12 Post-Infusion/Post-Injection Medication

Administer low-dose oral methylprednisolone (≤ 20 mg) or equivalent, the day after the daratumumab infusion/injection.

However, if a background regimen-specific corticosteroid (e.g., dexamethasone) is administered the day after the daratumumab infusion/injection, additional post-infusion/post-injection medications may not be needed. In addition, for any patients with a history of chronic obstructive pulmonary disease, consider prescribing post-infusion/post-injection medications such as anti-histamine, short and long-acting bronchodilators and inhaled corticosteroids. Following the first four infusions/injections, if the patient experiences no major infusion/injection reactions, these additional inhaled post-infusion/post-injection medications may be discontinued.

5.1.13 Prophylaxis for Herpes Zoster Reactivation following enrollment for all study subjects

Initiate antiviral prophylaxis to prevent herpes zoster reactivation on day 1 of daratumumab and continue for 3 months following treatment.

Management of Hepatitis B Virus Reactivation
Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation.

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.

5.1.14 Prophylaxis for Venous Thrombotic Events (VTE) while on lenalidomide:

Thromboprophylaxis is recommended (Table 5.1-4, Palumbo 2008). The regimen of thromboprophylaxis should be based on an assessment of the patient's underlying risks. Instruct patients to report immediately any signs and symptoms suggestive of thrombotic events. Erythropoiesis-stimulating agents (ESAs) and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision in patients receiving lenalidomide.

Table 5.1-4 Risk assessment model for the management of venous thromboembolism in multiple myeloma patients treated with thalidomide or lenalidomide

	Actions
Individual risk factors	
Obesity[a]	If no risk factor or any one risk factor is present:
Previous venous thromboembolism	Aspirin 81–325 mg once daily
Central venous catheter or pacemaker	
Associated disease	If two or more risk factors are present:
Cardiac disease	LMWH (equivalent of enoxaparin
Chronic renal disease	40 mg once daily)
Diabetes	Full-dose warfarin (target INR 2–3)
Acute infection	
Immobilization	
Surgery	
General surgery	
Any anesthesia	
Trauma	
Medications	
Erythropoietin	
Blood clotting disorders	
Myeloma-related risk factors	
Diagnosis	
Hyperviscosity	
Myeloma therapy	
High-dose dexamethasone[b]	LMWH (equivalent of enoxaparin 40 mg once daily)
Doxorubicin	Full-dose warfarin (target INR 2–3)
Multiagent chemotherapy	

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin.
[a]Obesity was defined as body mass index $\geqslant 30\,kgm^{-2}$.
[b]$\geqslant$480 mg per month.

5.1.15 Study drug records

Administration of study drug will be recorded by research personnel following completion of each infusion at the research center. For lenalidomide and dexamethasone, research subjects will receive a prescription containing sufficient pills to last for the next cycle. They will be instructed to keep a diary and bring empty bottles as well as any unused medication back to the research center. Research personnel will then reconcile the number of used and unused drug at each visit with the patient's diary.

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.2). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Dose adjustments should be made according to the system showing the greatest degree of toxicity.

1) Dose modifications are based on adverse events, which are possibly, probably or definitely related to drug. More than one dose reduction per cycle may occur.
2) If the AE is attributed to a specific drug, only that drug needs dose reduction.
3) Once a subject's dose has been reduced, no dose-re-escalation is permitted.
4) If AE improves to baseline or ≤ grade 1 prior to next scheduled dose, treatment should be restarted with a one dose level reduction for the remainder of the cycle. The next cycle will then continue with this reduced dose level.
5) For grade 3 or 4 AEs that are possibly, probably or definitely related to a particular agent(s) requiring dose modifications as per the tables in sections of individual agent below, will have that particular agent(s) held until resolution of the AE.
6) For grade 3 or 4 AEs that are possibly, probably or definitely related to a particular agent(s) which occur on or after the last treatment day of a cycle, will have that particular agent(s) reduced by one dose level beginning with the next cycle.
7) If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).
8) A delay of up to 14 days is allowed between cycles. Any delay beyond 14 days should be discussed with the study PI.
9) If there is a delay in obtaining lenalidomide for start of a new cycle, the cycle can be delayed until it is available in order to allow all drugs to be started at the same time. However, if the cycle has already started, lenalidomide should be started when it becomes available and continue for the remaining days of lenalidomide as per cycle.
10) All adverse events experienced by participants will be collected from the time of starting treatment through the study and until 30 days after completion of therapy. Participants continuing to experience toxicity beyond the follow-up periods noted above may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Dose adjustments for the drug combination are listed below. Drug specific dose reductions are listed in Sections 5.2.3, 5.2.4, and 5.2.5.

Table 5.2-1 Dose adjustments for the drug combination:

CTCAE AE Grade	Lenalidomide	Bortezomib
≥ Grade 3 neutropenia or ≥ Grade 3 febrile neutropenia	Refer to section 5.2.3 and table 5.2-2.	Refer to section 5.2.4.
Thrombocytopenia ≥ Grade 3 (platelets < 50,000/mm³)	Refer to section 5.2.3 and table 5.2-2.	Refer to section 5.2.4.

CTCAE AE Grade	Lenalidomide	Bortezomib
Non-blistering rash Grade 2-3 Grade 4	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level. Refer to table 5.2-2. Discontinue lenalidomide and do not resume.	No dose modifications required
Desquamating (blistering) rash - any Grade	Discontinue lenalidomide.	No dose modifications required
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide.	No dose modifications required
Sinus bradycardia / other cardiac arrhythmia Grade 2 Grade 3-4	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level. Refer to table 5.2-2. Discontinue lenalidomide	No dose modifications required
Renal Function CrCl < 30 mL/min	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level. Refer to table 5.2-2.	No dose modifications required
Venous Thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion after adequate anticoagulation (maintain dose level).	No dose modifications required
Hyperthyroidism or Hypothyroidism	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level). Refer to table 5.2-2.	No dose modifications required
Peripheral Sensory Neuropathy	No dose modifications required	Dose modification per table 5.2-4.
≥ grade 2 blood bilirubin increase	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21 restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level. Refer to table 5.2-2.	Hold (interrupt dose) and follow Biochemistry on days of scheduled bortezomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart bortezomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level.

CTCAE AE Grade	Lenalidomide	Bortezomib
≥ grade 2 ALT/AST increase	Hold (interrupt dose) and observe. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle until Day 21. Start next cycle at the reduced dose level. Refer to table 5.2-2.	Hold (interrupt dose) and follow Biochemistry on days of scheduled bortezomib doses. If the toxicity resolves to baseline or ≤ grade 1, restart bortezomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level
Any other ≥ grade 3 non-hematologic toxicity assessed as at least possibly related to the drugs (nausea, emesis and diarrhea included only if the grade persists despite maximal supportive care, only grade 4 fatigue included)	Hold (interrupt dose) and observe if toxicity is thought to be at least possible related to lenalidomide. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14, restart lenalidomide at next lower dose level and continue the cycle until Day 14. Start next cycle at the reduced dose level. Refer to table 5.2-2	Hold (interrupt dose) if toxicity is thought to be at least possible related to bortezomib. If the toxicity resolves to baseline or ≤ grade 1, restart bortezomib at next lower dose level and continue for rest of cycle as per protocol. Start next cycle at the reduced dose level. Refer to table 5.2-3.

5.2.1 Daratumumab

Individual dose modification of Dara SC/IV is not permitted. For managing Dara SC/IV-related toxicities, either a dose interruption or a dose delay is recommended.

ONLY if any of the following criteria are met and the event cannot be ascribed to lenalidomide, bortezomib, dexamethasone, or underlying MM, the Dara administration must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 hematologic toxicity (except for Grade 4 lymphopenia)
- Grade 3 or higher thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Grade 4 Neutropenia with any grade infection
- Grade 3 or higher nonhematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of Dara SC
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of Dara SC

Administration of Dara may be restarted upon recovery from toxicity to Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered.

If a dose is delayed, then the dates of all subsequent doses must be adjusted. Any AE deemed to be related to Dara that requires a dose hold of more than 28 days will be evaluated by the investigator to determine if further doses will be safe and efficacious.

5.2.2 Lenalidomide, bortezomib, and dexamethasone

General dose levels and toxicity-specific dose levels are in Sections 5.2.3, 5.2.4, and 5.2.5.

5.2.3 Lenalidomide

Hematological toxicity:
Induction/Consolidation/Maintenance

- Day 1: Hold for ANC <1000 (≥ Grade 3), Platelets <50,000 (≥ Grade 3)
- Subsequent treatment days: Hold for ANC < 500 (Grade 4), ≥ Grade 3 febrile neutropenia, and platelets < 25,000 (Grade 4)

If held:

1) Check CBCD twice weekly until ANC ≥ 1000 (resolved to ≤ Grade 2) and/or platelets ≥ 50,000 (resolved to ≤ Grade 2)
2) Resume lenalidomide and decrease by 1 dose level for remaining doses in cycle. If lower level dose lenalidomide is not available as planned, may follow institutional policy for resuming lenalidomide treatment*.

Table 5.2-2 Lenalidomide Dose Reduction Steps

Lenalidomide Dose Reduction Steps					
	For Induction and Consolidation			**For Maintenance**	
	CrCL ≥ 60 mL/min	*CrCL 30-60 mL/min*		*CrCL ≥ 60 mL/min*	*CrCL 30-60 mL/min*
Starting Dose	25 mg by mouth daily on Days 1-21	10 mg by mouth daily on Days 1-21	May increase to 15 mg once daily after 2 cycles if tolerating treatment	10 mg by mouth daily on Days 1-21	5 mg by mouth daily on Days 1-21
Dose level -1	20 mg	5 mg	10 mg	5 mg	2.5 mg
Dose level -2	15 mg	2.5 mg	5 mg	2.5 mg	Discontinue
Dose level -3	10 mg	Discontinue	2.5 mg	Discontinue	
Dose level -4	5 mg	Discontinue	Discontinue		
Dose level -5	Discontinue				

*If lower dose level prescription is not immediately available and patient has received Revlimid at the previous dosing level, treatment physician may decide if every other day dosing schedule is appropriate with the original dosing level until new prescription becomes available.

Non-hematological toxicities:
For other grade 3 and 4 toxicities judged to be related to lenalidomide, hold treatment and restart at physician's discretion at next lower dose level when toxicity has resolved to ≤ grade 2.

VTE prophylaxis: see section 5.1.10.

5.2.4 Bortezomib

Dose adjustments should be based on the highest grade of toxicity that is ascribed to bortezomib. Once the symptoms of toxicity have resolved, bortezomib therapy may be reinitiated at reduced dose per approved labeling, as follows:

Table 5.2-3 Bortezomib Dose Reduction Steps

Bortezomib Dose Reduction Steps	
Starting dose	1.5 mg/m^2
Dose level -1	1.3 mg/m^2
Dose level -2	1.0 mg/m^2
Dose level -3	0.7 mg/m^2
Dose level -4	Discontinue

Hematological toxicity:
Consolidation/Maintenance

- Day 1: Hold for ANC <1000 (≥ Grade 3), Platelets <50,000 (≥ Grade 3)
- Subsequent treatment days: Hold for ANC <500 (Grade 4), ≥ Grade 3 febrile neutropenia, and platelets <25,000 (Grade 4)

If held:

1) Check CBCD twice weekly until ANC ≥ 1000 (resolved to ≤ Grade 2) and/or platelets ≥ 50,000 (resolved to ≤ Grade 2)
2) Resume Bortezomib and decrease by 1 dose level for remaining doses in cycle

A dose of bortezomib may be delayed up to 48 hours. If a dose is delayed/held at any point in the cycle, then the dose is delayed and not skipped.. Two doses of Bortezomib have to be given at least 72 hours apart. If the subject experiences peripheral neuropathy, the dose adjustments should be made as outlined in Table 5.2-5.

Non-hematological toxicities:
Refer to table 5.2-1 for same holding parameters and/or dose adjustments for day 22.

Table 5.2-4 Recommended Dose Modification for Bortezomib-related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms [a]	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living [ADL][b])	Reduce bortezomib to 1 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL [c])	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m^2 once per week
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib

[a] Grading based on NCI Common Terminology Criteria CTCAE v5.0
[b] Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc.
[c] Self-care ADL (i.e. basic ADL): refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

5.2.5 Dexamethasone

Table 5.2-5 Dexamethasone Treatment Adjustment Steps

Dexamethasone Starting Dose	40 mg	20 mg
Dose level -1	20 mg	10 mg
Dose level -2	10 mg	4 mg
Dose level -3	4 mg	discontinue

Table 5.2-6 Treatment Guidelines for Dexamethasone Toxicities

Body System	Toxicity	Recommended Action
Cardiovascular	≥ Grade 3 edema (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed and restart dexamethasone at 1 dose decrement; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Gastrointestinal	Grade 1-2 dyspepsia, gastric or duodenal ulcer, gastritis (requiring medical management)	Treat with H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone by one dose level.
	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart at 1 dose decrement along with concurrent therapy with H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone permanently
	Acute pancreatitis	Discontinue dexamethasone permanently
Metabolic	≥ Grade 3 hyperglycemia	Treatment with insulin or PO hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.
Musculoskeletal	≥ Grade 2 muscle weakness (symptomatic and interfering with function ± interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Neurology	≥ Grade 2 confusion or mood alteration (interfering with function ± interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart at 1 dose decrement. If symptoms persist despite above measures, discontinue dexamethasone permanently

5.3 Concomitant Medications/Treatments

The following pre-study therapies given at any time before first dose of study treatment must be recorded at screening: steroids of any dose or duration given for MM or radiation therapy for MM.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed per Investigator's Brochure (IB) or package inserts. The sponsor must be notified in advance (or as soon as possible thereafter of any instances in which prohibited therapies are administered). Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Systemic use of the following concomitant medications will be collected in the case report form (CRF) and recorded in the source documents beginning with signing of the informed consent form (ICF) to 30 days after the last dose of the last study treatment or until the start of next-line anticancer treatment, if earlier: growth factors, transfusions, anti-infective medications (antibacterials, antivirals, and antimycrotics), steroids, anti-arrhythmic medications and other cardiac supportive therapy, anti-epileptic medications, centrally acting psychiatric medications, anti-histamines and other medications targeting post-infusion systemic reactions, and any anticancer therapy (including radiation as noted below).

5.4 Other Modalities or Procedures

Radiation therapy to a localized mass while participant is on study treatment is acceptable with prior approval of the Sponsor-Investigator.

5.5 Duration of Therapy

This is a study based on adaptive design for decision making of treatment options. Duration of therapy (daratumumab cycles) will depend on individual approach, response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Adverse event
- Protocol violation / subject non-compliance
- Lost to follow-up
- Progressive disease
- Study terminated
- Subject no longer consents to participate in the study
- Pregnancy or suspected pregnancy
- Delay in treatment >28 days due to unrecovered toxicity unless treating investigator considers continued therapy to be in the subject's best interest and approval is granted by the Sponsor-Investigator

5.6 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.5 above apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.7. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.7 Duration of Follow-Up

Participants will be followed every three months (+/- 1 month) until death or for up to 3 years after the last patient has been enrolled. Participants removed from study treatment for unacceptable adverse events will be followed for resolution or stabilization of the adverse event. Follow-up may be conducted in-person, remotely (i.e., phone call, etc.), or from medical records review.

For patients who discontinue study treatment for any reason, information from patients' medical records and consult with their healthcare providers will be obtained including disease assessment (if patients have not progressed) and other lines of therapy received.

There is no exclusion (wash-out) period at the end of the study before start of another treatment.

5.8 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

- Patient withdraws consent (termination of treatment and follow-up)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment
- Patient is unable to comply with protocol requirements;
- Treating physician determines that continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- Lost to follow-up;
- Termination of the study by The University of Michigan;
- Patient completes protocol treatment and follow-up criteria.

If the reason for withdrawal is the occurrence of an AE, the subject will be followed until such events resolve, stabilize, and, according to the Treating Investigator's judgment, there is no need of further follow-up. The reason for withdrawal from the study will be documented in the CRF.

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

5.9 Patient Replacement

Patients who receive at least one cycle of induction therapy but subsequently withdraw or otherwise remove consent prior to achieving their primary endpoint will in general be analyzed, specifically, counted as MRD-positive, for purposes of the primary analysis and not replaced, unless there is compelling evidence that the patient's reason for withdrawal was entirely unrelated to the receipt of therapy, including any adverse events.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

The Time and Events table (table 6.2) summarizes the frequency and timing of study procedures and assessments applicable to this study.

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures (including bone marrow aspiration and biopsy, echo, PET/CT or MRI) must be performed within 45 days of starting protocol treatment unless otherwise stated.

The Investigator is responsible for keeping a record of all participants screened for entry into the study and subsequently excluded. The reason(s) for exclusion must also be recorded. Results of bone marrow biopsy, MRI, and PET/CT scans within 45 days of initiation of protocol therapy may be used to fulfill screening requirements.

6.2 Time and Events Table

	Screening Phase [a]	Treatment Phase																		Follow-up Phase [c]
		Induction Dara-Rd (28 day cycles)						MRD 1 [r]	Stem Cell Collection	Consolidation Dara-RVd (28 day cycles)				MRD 2[r]	ASCT	Maintenance [v] Dara-R (28 day cycles)	MRD 3[r]	Maintenance R (28 day cycles)	EOT [b]	
		Cycles 1-2 (week 1-8)				Cycles 3-6 (week 9-24)				Cycles 7-9 (week 25-36)						Cycles 10-22 (weeks 37-88)		Cycle 23- Every 3 months		
		D1	D8	D15	D22	D1	D15			D1[v]	D8	D15	D22			D1[v]		D1[v]		
Screening:																				
Informed consent& Inclusion/Exclusion criteria	X																			
Complete medical history	X																			
Vitals [d]/Weight/ BSA/Height [e]	X	X				X				X						X		X	X	
Physical examination [t]	X	X				X				X						X		X	X	
ECOG performance status	X	X				X				X						X		X	X	
Forced expiratory volume test [f]	X																			
12-lead ECG [g]	X																			
Echo	X																			
Hematology [h]	X	X	X	X	X	X	X			X	X	X	X			X		X	X	
Coagulation [i]	X																			
Biochemistry [j]	X	X				X				X						X		X	X	
ABO/Rh blood type assessment [p]	X																			
Urinalysis (SOC)	X																			
Serum/Urine pregnancy test [k]	X	X				X				X						X		X	X	
HIV, Hep B/C serologies	X																			
HBV DNA testing [z]	X	Every 12 weeks during treatment, at EOT and every 12 weeks for up to 6 months after the last dose of study treatment.																		

	Screening Phase [a]	Treatment Phase																		Follow-up Phase [c]
		Induction Dara-Rd (28 day cycles)						MRD 1 [r]	Stem Cell Collection	Consolidation Dara-RVd (28 day cycles)				MRD 2 [r]	ASCT	Maintenance [v] Dara-R (28 day cycles)	MRD 3 [r]	Maintenance R (28 day cycles)	EOT [b]	
		Cycles 1-2 (week 1-8)				Cycles 3-6 (week 9-24)				Cycles 7-9 (week 25-36)						Cycles 10-22 (weeks 37-88)		Cycle 23- Every 3 months		
		D1	D8	D15	D22	D1	D15			D1 [v]	D8	D15	D22			D1 [v]		D1 [v]		
Disease Assessment:																				
Serum M-protein (S-PEP) [s]	X	X				X				X						X		X	X	
Serum Immunofixation (sIFE) [s]	X	X				X				X						X		X	X	
Urine M-protein (U-PEP)[u]	X	X				X				X						X		X	X	
Urine Immunofixation (uIFE) [u]	X	X				X				X						X		X	X	
Serum Free light chain (FLC)	X	X				X				X						X		X	X	
Serum Immunoglobulins	X	X				X				X						X		X	X	
B2-MG & LDH	X	X				X				X						X				
BM aspiration/ biopsy procedure	X							X[r]						X[r]			X[r]			
BM histology/IHC	X							X						X			X			
BM CyG/karyotyping	X							X						X			X			
BM FISH [q]	X							X						X			X			
BM flow cytometry	X							X						X			X			
Baseline PET/CT (preferred) or MRI (alternative) [l]	X																			
MRD Assessment:[cc]																				
BM NGS MRD [s]	X							X						X			X			
Imaging MRD PET/CT (preferred) or MRI (alternative) [l]								X						X			X			
Research Samples:																				
BM research sample[bb]	X							X						X			X			

	Screening Phase [a]	Treatment Phase																	Follow-up Phase [c]
		Induction Dara-Rd (28 day cycles)						MRD 1 [r]	Stem Cell Collection	Consolidation Dara-RVd (28 day cycles)				MRD 2 [r]	ASCT	Maintenance [v] Dara-R (28 day cycles)	MRD 3 [r]	Maintenance R (28 day cycles)	EOT [b]	
		Cycles 1-2 (week 1-8)				Cycles 3-6 (week 9-24)				Cycles 7-9 (week 25-36)						Cycles 10-22 (weeks 37-88)		Cycle 23- Every 3 months		
		D1	D8	D15	D22	D1	D15			D1[v]	D8	D15	D22			D1[v]		D1 [v]		
PBMC/Stool research samples	X							X						X			X		X	
Additional Procedures:																				
Stem Cell Mobilization [x]								X												
ASCT															x					
Study Drug Dosing:																				
Daratumumab 16mg/kg IV/SQ at 1800mg		X	X	X	X	X	X			X						X[m] Every other cycle				
Pre- and post-infusion/injection medications Dexamethasone Montelukast [aa] Acetaminophen Anti-histamine		X	X	X	X	X	X			X						X				
Lenalidomide [w]		Lenalidomide 25 mg po Days 1-21/Cycle								Lenalidomide 25 mg po Days 1-21/cycle						Lenalidomide 10 mg po daily Days 1-21/cycle		Lenalidomide 10 mg po daily Days 1-21/cycle		
Dexamethasone [n]		X	X	X	X	X	X			X										
Bortezomib 1.5mg/m^2 SQ										X	X	X	X							
Study Drug Compliance and Safety Review:																				
Adverse event monitoring		Continuous from time of ICF until 30 days after last study treatment (Dara, R, V, or d) dose																		
REMS® patient compliance review		X				X				X						X		X		
Patient medication diary review		X				X				X						X		X		
Patient Reported Outcomes: [o]																				
FACT GOG-Ntx	X	X				X				X						X		X	X	
EQ-5D-5L	X	X				X				X						X		X	X	

	Screening Phase [a]	Treatment Phase																		Follow-up Phase [c]
		Induction Dara-Rd (28 day cycles)						MRD 1 [r]	Stem Cell Collection	Consolidation Dara-RVd (28 day cycles)				MRD 2 [r]	ASCT	Maintenance [v] Dara-R (28 day cycles)	MRD 3 [r]	Maintenance R (28 day cycles)	EOT [b]	
		Cycles 1-2 (week 1-8)				Cycles 3-6 (week 9-24)				Cycles 7-9 (week 25-36)						Cycles 10-22 (weeks 37-88)		Cycle 23- Every 3 months		
		D1	D8	D15	D22	D1	D15			D1 [v]	D8	D15	D22			D1 [v]		D1 [v]		
COVID-19 Survey	X							X						X			X			
Follow-up:																				
Subsequent therapy/ Survival/ Secondary malignancy																				X [c]

Abbreviations:
COPD=chronic obstructive pulmonary disease
CR=complete response
CT=computed tomography
D1C1=day 1, cycle 1
DRVd=daratumumab, Revlimid (lenalidomide), Velcade (bortezomib), dexamethasone
ECOG=Eastern Cooperative Oncology Group
EOT=End-of-Treatment
FLC=free light chain
FUP=Follow-up Phase
ICF=informed consent form
IV=intravenous
QIg=quantitative immunoglobulins
MRD=minimal residual disease
MRI=magnetic resonance imaging
PBMCs=peripheral blood mononuclear cells
PK=pharmacokinetics
PD=progressive disease
PFS=progression-free survival
PRO=patient-reported outcomes
R-ISS=revised international staging system
SAE=serious adverse event
SQ=subcutaneous

Note:
Study treatment is defined as daratumumab, lenalidomide, bortezomib (as needed), and dexamethasone.

a) Assessments required at screening visit, except for hematology, do not have to be repeated if performed ≤ 7 days prior to Cycle 1 Day 1 unless otherwise specified. To take into account scheduling conflicts (e.g., over public holidays), a ± 3-day window will be allowed for all assessments and treatments, unless otherwise specified. Following Cycle 2, a 7 day + window is permitted between cycles. However, every effort must be made to follow the schedule outlined in the above table.
b) EOT: Important for correlative study sample collections. To occur 28 days ± 14 days from last dose of study treatment or prior to start of subsequent therapy if sooner.
c) Follow-up may be conducted in-person, remotely (i.e., phone call, etc.), or from medical records review and will be performed once every three months (+/- 1 month). Information obtained during follow-up includes survival status, subsequent anti-cancer treatment, response to subsequent anticancer treatment, and information on secondary malignancies, etc. For patients who discontinued study treatment for any reason, information from their medical records and consult with their healthcare providers will be obtained including disease assessments and other anti-cancer treatment received.
d) Vitals signs (blood pressure, temperature, heart rate) to be measured according to institutional standards unless otherwise specified. Subjects who experience an infusion reaction require vital signs to be monitored per institutional guidelines
e) Height required at baseline only. BSA is to be calculated based on body weight in accordance with institutional standards.
f) Forced expiratory volume test: for subjects with COPD or asthma.
g) ECG: 12-lead ECG at baseline and as clinically indicated.
h) Hematology includes the following parameters: complete blood count consisting of a total white blood cell count with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin; hematocrit and platelet count. Hematology assessments should be performed on the scheduled day or up to three days prior, even if study medication is being held. More frequent examinations may be performed at the Investigator's discretion, if medically indicated.
i) Coagulation includes: prothrombin time (PT)/international normalized ratio (INR), activated partial thromboplastin time (aPTT) to be performed during the screening period and otherwise as clinically indicated.
j) Biochemistry includes the following parameters: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, LDH, C-reactive protein, and β2 microglobulin. In addition, thyroid-stimulating hormone (TSH) and free thyroxine (T4) collected at Screening and each MRD assessment. Additionally, a hepatitis panel including hep B and C should be performed at screening. If active disease at baseline, the patient's disease followed every 3 months during treatment until 6 months after the end of treatment.
k) Pregnancy testing (serum or urine) will be performed in pre-menopausal women and women who are post-menopausal for < 2 years per REMS program (two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles).
l) PET/CT: May be within 45 days of planned treatment start (does not need to be repeated if within 45 days).
m) Daratumumab maintenance dosing: every 8 weeks.
n) Dexamethasone dosing:40 mg IV or PO/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5 or the patient cannot tolerate the higher dose). On daratumumab infusion/injection days, 20 mg of the dexamethasone dose will be given as a pre-infusion/pre-injection medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose will be given as a daratumumab pre-infusion/pre-injection medication.
o) Patient Reported Outcomes are collected as specified in the study calendar. Includes Neurotoxicity Questionnaire (Appendix C) and Patient reported survey (EQ-5D, Appendix D).
p) ABO/Rh blood type assessment: Please see section 8.1.2.5

q) FISH panel for myeloma: FISH for myeloma panel from each institutional pathology lab, Mayo clinic lab and commercialized labs (e.g., LabCorp) are all acceptable. Mayo lab FISH for myeloma testing algorithm can be found at https://www.mayomedicallaboratories.com/test-catalog/Overview/35292. Tissue must be submitted for FISH analysis prior to study enrollment. However, the FISH report is not required prior to participant enrollment and may be provided to the Coordinating Center until C2D1. In addition, if there is insufficient tissue for FISH analysis, the FISH screening requirement may be waived.

r) MRD: At screening: for Clonality ID; MRD1: bone marrow procedure within 1 week before completion of induction and 2 weeks after; MRD2: bone marrow procedure within 1 week before completion of consolidation and 2 weeks after; MRD3: bone marrow procedure within 1 week before completion of 1 year of maintenance and 2 weeks after. MRD detection includes both bone marrow MRD in bone marrow biopsy and imaging MRD (PET/CT or MRI if PET/CT is not approved by insurance). For bone marrow MRD clonality (ID) and MRD (tracking) tests, please follow the sample requirement from Adaptive ClonoSEQ https://www.clonoseq.com/resources-and-support/downloadable-resources/. **It is necessary to verify that the test specimen meets sample requirement before enrollment.**

s) SPEP/SIFE: Once started on daratumumab treatment, SPEP/SIFE should be sent to a lab (either institutional or commercialized lab such as Mayo clinic lab, LabCorp) who is able to distinguish the band of daratumumab from monoclonal protein at C6D1, C9D1, and C22D1. Otherwise, sites may use their institutional standard of care SPEP/SIFE at all other study time points.

t) Physical Exam should include 1) evaluation for plasmacytoma and 2) a general neuro exam focusing on sensory peripheral neuropathy at screening and each subsequent visit if presence of signs or symptoms. If plasmacytoma is detected on physical examination or PET/CT at baseline, follow-up should be performed during therapy and documented.

u) U-PEP and UIFE to be completed at screening and repeated throughout treatment course only if measurable disease at baseline, until undetected. Once measurable disease is undetectable, patients will no longer have U-PEP and UIFE collected except at C6D1 (MRD1) C9D1 (MRD2), and C22D1 (MRD3). For patients who only have measurable disease via urine at screening, continue to have U-PEP and UIFE completed throughout treatment course even if measurable disease becomes undetectable. U-PEP and UIFE are collected at time of disease progression for all patients regardless of status of measurable disease at baseline.

v) If disease progression (PD per IMWG response criteria) is documented for two times consecutively, regardless of MRD status, patient will be removed from active study treatment per treating physician.

w) Lenalidomide dose adjustment in patients with renal insufficiency per Sections 5.1

x) Patients can mobilize stem cells any time following 4 to 6 cycles of induction therapy. If stem cells are harvested, interruption of treatment cycles for up to 28 days is allowed for completion of stem cell collection. While stem cell collection is strongly encouraged for transplant eligible patients, it is not required for protocol participation.

y) Maintenance therapy should start between days 60-100 post-ASCT.

z) 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.

aa) Refer to section 5.1.11 regarding montelukast. Use only for doses 1-4. In the case of lenalidomide (Revlimid) insurance approval delay, the treating investigator may initiate systemic treatment to avoid organ damage from the underlying disease. All efforts must be made to avoid this delay.

bb) Bone marrow is required at disease progression for correlative studies.

cc) MRD is only obtained if VGPR or CR at each MRD time point.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect

Responses to treatment will be documented both clinically and hematologically. To determine the disease response to treatment, review the following lab and clinical data:

- Anatomic Pathology- Bone marrow/tissue/lymph node biopsies
- Lab values pertinent to disease (e.g., SPEP/UPEP/SIFE, sFLC for myeloma)
- Hematology and Chemistry lab values
- Flow Cytometry
- Cytogenetics
- Cytology
- Immunology/Serology
- Molecular Diagnostics
- PET/CT/MRI/X-Ray
- Clinical signs and symptoms as documented in physician clinical notes

Disease staging will be performed according to International Myeloma Working Group (IMWG) response criteria. The updated criteria for CR require the absence of an M-protein on serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE) (Palumbo, Rajkumar et al. 2014).

7.1.1 Disease Parameters

7.1.1.1 Measurable disease

Please see section 3.1.6 for definition of measurable disease.

7.1.1.2 Methods for Evaluation of Measurable Disease

All baseline evaluations should be performed on Cycle 1, Day 1 of initial therapy with DaraRd. Response will be assessed by M-protein quantification, protein electrophoresis and immunofixation from serum and a 24-hour urine collection. In addition, bone marrow aspiration and biopsy will be performed to determine overall response and MRD status.

The same method of assessment and technique should be used for disease measurement at baseline and during follow-up.

7.1.2 Response Criteria

A six-week confirmation measurement for disease response assessments is required in this protocol.

7.1.2.1 International Myeloma Working Group Response Criteria

Response criteria for all categories and subcategories of response except CR are applicable only to patients who have 'measurable' disease, as defined in Section 7.1.1.1. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are required to satisfy these response requirements for MRD negativity.

Sustained MRD negativity: MRD negativity in the bone marrow and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative at 5 years).

Bone Marrow MRD negativity: by NGS MRD as approved by the FDA (https://www.fda.gov/news-events/press-announcements/fda-authorizes-first-next-generation-sequencing-based-test-detect-very-low-levels-remaining-cancer).

Imaging plus MRD negativity: defined by NGS plus one of the following: 1) disappearance of every area of increased tracer uptake found at baseline or 2) a proceeding PET/CT or 3) decrease to less mediastinal blood pool standardized uptake value (SUV) or 4) decrease to less than that of surrounding normal tissue.

Stringent CR: CR as defined below plus normal free light chain ratio and absence of clonal cells in bone marrow* by immunohistochemistry or immunofluorescence.**
*Confirmation with repeat bone marrow biopsy is not needed.
**Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of > 4:1 or < 1:2.

CR: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow.*
*Confirmation with repeat bone marrow biopsy is not needed.

Very good partial response (VGPR): Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours.

Partial response (PR): > 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by > 90% or to < 200 mg per 24 hours. If the serum and urine M-protein are unmeasurable, a > 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (definition of measurable disease in Section 7.1.1.1). If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, > 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30%. In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required.

Stable disease (SD): Not meeting criteria for CR, VGPR, PR or progressive disease. This is not recommended as an indicator of response; stability of disease is best described by providing the time to progression estimates.

Progression (PD): > 25% increase of serum M-protein (which must also be an absolute increase of >0.5 g/dL) and/or urine M-protein (which must also be an absolute increase of > 200 mg/24hr). If serum and urine M-protein are unmeasurable, there must be an absolute increase of > 10 mg/dL between involved and uninvolved FLC levels. PD is also measured by an absolute increase in bone marrow plasma cells > 10%. In addition to the above listed criteria, progression may also be measured by a definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas or development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.

7.1.2.2 Duration of Response and Endpoint Definitions

Duration of overall response: The duration of overall response is measured as the time from initiation of first response to first documentation of disease progression or death.

Patients who have not progressed or died are censored at the date last known progression-free.

Duration of overall complete response: The duration of overall CR is measured as the time from initiation of CR to first documentation of disease progression or death. Patients who have not progressed or died are censored at the date last known progression-free.

Time to progression (TTP): Time to progression is defined as the time from study enrollment until progression. Patients who have died without evidence of progression are censored in the TTP analysis at the time of death and patients who are alive without progression are censored at the last disease assessment.

Overall survival (OS): OS is defined as the time from randomization to death. Alive patients are censored at the date last known alive.

7.1.3 Progression-Free Survival

Progression-Free Survival (PFS): time from study enrollment to the disease progression or death from any cause. Patients who have not progressed or died are censored at the date last known progression-free.

7.2 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 5 for reporting of non-hematologic adverse events.

8.0 ADVERSE REACTIONS

8.1 Daratumumab

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.1.1 Contraindications

Patients with a history of severe hypersensitivity to daratumumab, hyaluronidase, or any of the excipients.

8.1.2 Special Warnings and Precautions for Use

8.1.2.1 Infusion Related Reactions (IRR)

Daratumumab can cause severe infusion reactions including anaphylaxis reactions. These reactions can be life-threatening and fatal outcomes have been reported. Approximately half of all patients experienced a reaction, most during the first infusion and were Grade 1 to 2.

Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing daratumumab. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

Severe reactions include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt daratumumab infusion for reactions of any severity and institute medical management as needed. Permanently discontinue daratumumab therapy for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following daratumumab infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long- acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease. See management of IRR in Section 5.0 of the protocol.

8.1.2.2 Neutropenia

Daratumumab may increase neutropenia induced by background therapy.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Daratumumab dose delay may be required to allow recovery of neutrophils. No dose reduction of daratumumab is recommended. Consider supportive care with growth factors.

8.1.2.3 Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Daratumumab dose delay may be required to allow recovery of platelets. No dose reduction of daratumumab is recommended. Consider supportive care with transfusions.

8.1.2.4 Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

8.1.2.5 Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum (Chapuy, Nicholson et al. 2015). The determination of a patient's ABO and Rh blood type are not impacted.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received daratumumab. Type and screen patients prior to

dosing with daratumumab. The subject should be provided with his/her blood type information for reference.

8.1.2.6 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 820 patients with MM including 526 patients from two Phase 3 active-controlled trials who received DARZALEX in combination with either lenalidomide (DRd, n=283; Study 3) or bortezomib (DVd, n=243; Study 4) and five open-label, clinical trials in which patients received DARZALEX either in combination with pomalidomide (DPd, n=103; Study 5), in combination with lenalidomide (n=35), or as monotherapy (n=156).

Combination Treatment with Lenalidomide

Adverse reactions described in Table 8.1-1 reflect exposure to DARZALEX (DRd arm) for a median treatment duration of 13.1 months (range: 0 to 20.7 months) and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide group (Rd) in Study 3. The most frequent adverse reactions (≥20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. The overall incidence of serious adverse reactions was 49% for the DRd group compared with 42% for the Rd group. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each). Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 8.1-1 Adverse reactions reported in >=10% of patients and with at least a 5% frequency greater in the DRd arm in Study 3

Adverse Reaction	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 8.1-2.

Table 8.1-2: Treatment-emergent hematology laboratory abnormalities in Study 3

	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

Key: D=Daratumumab, Rd=lenalidomide-dexamethasone.

Combination Treatment with Bortezomib

Adverse reactions described in Table 8.1-3 reflect exposure to DARZALEX (DVd arm) for a median treatment duration of 6.5 months (range: 0 to 14.8 months) and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib group (Vd) in Study 4. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group. Serious adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each). Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Table 8.1-3: Adverse reactions reported in ≥ 10% of patients and with at least a 5% frequency greater in the DVd arm in Study 4

Adverse Reaction	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	45	9	0	0	0	0
Gastrointestinal disorders						
Diarrhea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Edema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[c]	44	6	0	30	3	< 1
Nervous system disorders						
Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[d]	27	0	0	14	0	0
Dyspnea[e]	21	4	0	11	1	0

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see description of Infusion Reactions below.

[b] edema peripheral, edema, generalized edema, peripheral swelling

[c] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[d] cough, productive cough, allergic cough

[e] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 8.1-4.

Table 8.1-4: Treatment-emergent hematology laboratory abnormalities in Study 4

	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	<1
Lymphopenia	89	41	7	81	24	3

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

Monotherapy

The safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory MM treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.04 months). Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%). Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 8.1-5.

Table 8.1-6 describes Grade 3--4 laboratory abnormalities reported at a rate of ≥10%.

Table 8.1-5: Adverse reactions with incidence ≥10% in patients with multiple myeloma treated with DARZALEX 16 mg/kg

	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see below.

[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.

Table 8.1-6: Treatment emergent Grade 3-4 laboratory abnormalities (≥10%)

	Daratumumab 16 mg/kg (N=156)		
	All Grade (%)	Grade 3 (%)	Grade 4 (%)
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

Infusion Reactions
In clinical trials (monotherapy and combination treatments; N=820) the incidence of any grade infusion reactions was 46% with the first infusion of DARZALEX, 2% with the second infusion, and 3% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion reaction with second or subsequent infusions. The median time to onset of a reaction was 1.4 hours (range: 0.02 to 72.8 hours). The incidence of infusion modification due to reactions was 42%. Median durations of infusion for the 1st, 2nd and subsequent infusions were 7.0, 4.3, and 3.5 hours respectively. Severe (Grade 3) infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions (any Grade, ≥5%) were nasal congestion, cough, chills, throat irritation, vomiting and nausea.

Herpes Zoster Virus Reactivation
Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the randomized controlled combination therapy studies, herpes zoster was reported in 2% each in the DRd and Rd groups (Study 3), in 5% versus 3% in the DVd and Vd groups (Study 4) and in 2% of patients receiving DPd (Study 5).

Infections
In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported with DARZALEX combinations and background therapies (DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%; DPd: 28%). Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. Discontinuations from treatment were reported in 3% versus 2% of patients in the DRd and Rd groups respectively, 4% versus 3% of patients in the DVd and Vd groups respectively, and in 5% of patients receiving DPd. Fatal infections were reported in 0.8% to 2% of patients across studies, primarily due to pneumonia and sepsis.

Post marketing experience:
The following adverse reactions have been identified during post-approval use of daratumumab (frequency is not reported): anaphylaxis reaction, pancreatitis and infections (Cytomegalovirus, Listeriosis).

8.1.2.7 Other Clinical Trial experience

Following the administration of daratumumab and daratumumab and hyaluronidase for SC injection, syncope was reported.

8.1.2.8 Geriatric use

In patients that received daratumumab and hyaluronidase in combination with pomalidomide or lenalidomide and dexamethasone, adverse reactions occurring at a

higher frequency (> or equal to 5% difference) in patients 65 years of age or older included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (> or equal to 2% difference) in patients 65 years of age and older included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

8.1.3 Interaction with Other Medications

Drug Interactions

Effect of other drugs on daratumumab
The co-administration of lenalidomide or bortezomib with daratumumab did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs

The co-administration of daratumumab with lenalidomide or bortezomib did not affect the pharmacokinetics of lenalidomide or bortezomib.

8.1.4 Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by IMWG criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 633 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 628 patients developed treatment-emergent anti-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

8.2 Bortezomib

For the most recent safety update, please refer to the current Agent Prescribing Information.

8.2.1 Contraindications

Patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions.

8.2.2 Special Warnings and Precautions for Use

- Peripheral Neuropathy: Manage with dose modification or discontinuation. Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment.
- Hypotension: Use caution when treating patients taking anti-hypertensives, with a history of syncope, or with dehydration.
- Cardiac Toxicity: Worsening of and development of cardiac failure has occurred. Closely monitor patients with existing heart disease or risk factors for heart disease.
- Pulmonary Toxicity: Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms.
- Posterior Reversible Encephalopathy Syndrome: Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected.
- Gastrointestinal Toxicity: Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement.
- Thrombocytopenia or Neutropenia: Monitor complete blood counts regularly throughout treatment.
- Tumor Lysis Syndrome: Closely monitor patients with high tumor burden.
- Hepatic Toxicity: Monitor hepatic enzymes during treatment.
- Embryo-fetal Toxicity: VELCADE can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy.
- Thrombotic Microangiopathy: Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) have been reported in the postmarketing setting in patients who received bortezomib. Monitor for signs and symptoms of TTP/HUS. Discontinue bortezomib, if suspected

8.2.3 Adverse Reactions in Clinical Trials

Most commonly reporting adverse reactions (incidence ≥20%) in clinical trials include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.

8.3 Lenalidomide

For the most recent safety update, please refer to the current Agent Prescribing Information.

8.3.1 Contraindications

- Females who are pregnant

- Patients who have demonstrated severe hypersensitivity to lenalidomide

8.3.2 Special Warnings and Precautions for Use

- Allergic Reactions, including fatalities: Hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis; discontinue REVLIMID if reactions are suspected. Do not resume REVLIMID if these reactions are verified.
- Tumor lysis syndrome (TLS) including fatalities: Monitor patients at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions.
- Tumor flare reaction: Serious tumor flare reactions have occurred during investigational use of REVLIMID for chronic lymphocytic leukemia and lymphoma.
- Hepatotoxicity: Hepatic failure including fatalities; monitor liver function. Stop REVLIMID and evaluate if hepatotoxicity is suspected.
- Second Primary Malignancies (SPM): Higher incidences of SPM were observed in controlled trials of patients with multiple myeloma receiving REVLIMID.

8.3.3 Adverse Reactions in Clinical Trials

Multiple myeloma: Most common adverse reactions (≥20%) include fatigue, neutropenia, constipation, diarrhea, muscle cramp, anemia, pyrexia, peripheral edema, nausea, back pain, upper respiratory tract infection, dyspnea, dizziness, thrombocytopenia, tremor and rash.

9.0 Sponsor Responsibilities

9.1 Health Authority

As the sponsor of the Study and to the extent required by any applicable laws or regulations in each country/territory, the Institution/Investigator shall be solely responsible for complying, within the required timelines, with any safety reporting obligation towards the competent health authorities, the Ethics Committees (EC) or Independent Review Board (IRB) and the participating (co- or sub-) investigators.

9.2 General

The Institution / Investigator shall notify Company immediately in case of a suspension of recruitment or premature stop of the concerned clinical study because of a safety concern; preferably by means of a telephone contact with the Company Representative, alternatively by email within twenty-four (24) hours of the decision.

Institution / Investigator shall provide to the Company copies of any and all relevant extraordinary* (not including routine initial or follow-up ICSR submission) correspondences with health authorities and ethics committees regarding any and all serious adverse events (irrespective of the association with the Janssen Product(s) Under Study). Copies of such correspondence shall be provided within 24 hours of such report or correspondence being sent to applicable health authority.
*See definitions section 4.6

Training: Institution/Sponsor of the Study shall be responsible for training the Study personnel (including the Investigator) on managing safety information arising from the Study according to agreed procedures and the requirements of this Agreement.

Management of Safety Data: The Institution and Investigator will provide safety information arising from the Study to the Company on adverse events, special situations including pregnancies and product quality complaints as defined within this exhibit. This safety information will be documented by the Investigator and reported as described in this exhibit from the time a subject has signed and dated an Informed Consent Form (ICF) until 30 days after the last dose of the Janssen Product(s) Under Study. All subsequent AEs and SAEs beyond 30 days after the last dose of the Janssen Product(s) under study shall be collected/reported if the investigator considers the AE/SAE to be causally related to the use of the Janssen Product(s) Under Study.

For the purposes of this Study, the Janssen Product(s) Under Study is (are):

DARZALEX™ (daratumumab-IV)
FASPRO™ (daratumumab-SC)

Maintenance of Safety Information: All safety data arising from the Study shall be maintained in a clinical database in a retrievable format. The Institution and Investigator shall provide a summary of all non-serious adverse events (NSAES) annually, and both serious and non-serious adverse events will be summarized in the final Study report (excluding those from subjects not exposed to a Janssen product). The summary shall include a listing of: Patient ID, adverse event term (uncoded), severity, relationship to Janssen Product(s) Under Study, and action taken with Janssen Product(s) Under Study. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the safety data shall be made available within a reasonable timeframe at the Company's request.
Follow-up: All (serious and non-serious) adverse events reported for a Janssen Product(s)Under Study shall be followed up in accordance with good clinical practice (GCP).
If batch/lot number is available, it must be reported. If batch/lot number is not available, it must be documented that it is not available. Without this documentation, Company is required to perform two follow-up attempts to obtain the batch/lot number.

9.3 Reporting of Safety data and Product Quality Complaints (PQCs) to Company

All adverse events and special situations, whether serious or non-serious, related or not related, collected as per protocol design, following exposure to a Janssen Product(s) Under Study 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 evaluation concerning the relationship of the adverse event to a Janssen Product(s) Under Study.

The Institution will submit (and procure that the Investigator submits), to the identified Company Representative in each Country/Territory the following safety information:

Type of report	Timelines	How to report
Serious Adverse Event, including SAE related to the device (when the Janssen Product(s) under study is a combination product)	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Adverse Events of Special Interest (AESI)	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Reports of drug exposure during pregnancy (maternal and paternal), with or without SAE.	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Pregnancy Notification Form/Serious Adverse Event Form.
Reports of Suspected transmission of any infectious agent via administration of a Janssen Product, with or without an SAE	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Abnormal Pregnancy Outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy)	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.

Special Situation (SS), if associated with an SAE	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties, on a Serious Adverse Event Form.
Special Situation (not associated with an SAE)	Annually and in final study report.	Recorded in CRF and reported annually and in final study report.
Product Quality Complaints, including adverse device effects and device malfunctions, (when the Janssen Product(s) under study is a combination product)	Within 3 business days of becoming aware of the event(s)	By a secure means, as agreed by the Parties.
Non-Serious Adverse Event* (*Not meeting other listed 3 business day reporting criteria e.g. AESI or SS)	Annually and in final study report.	Recorded in CRF and reported annually and in final study report.
Follow-up information	Transmitted within the same timeframes as above i.e. if initial report was required to be submitted within 3 business days, follow-up information shall be submitted within the same timeframe.	Transmitted via same method as above i.e. if initial method of transmission was on an SAE form, follow-up information shall be transmitted in the same manner.

The Institution and/or 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.
Note: In the event the Study is blinded, the Investigator will submit an unblinded SAE or pregnancy exposure report to Company.
If the Investigator/agent of the Investigator receives safety information and is aware it involves a non-study J&J product, it will be reported to Company, indicating it is an incidental spontaneous report discovered during the course of the study.
Pregnancy:
If a subject becomes pregnant during the study, in addition to reporting the pregnancy within 3 business days, a determination regarding Janssen Product(s) Under Study discontinuation and subject discontinuation must be made by the investigator in alignment with the protocol inclusion/exclusion criteria and in consultation with the reference safety information.
Because the effect of the Janssen Product(s) Under Study on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen Product(s) Under Study will be reported by the Investigator within 3 business days **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.

9.4 Sponsor confirmation/review of SAEs

Company Representative or designee will provide the Institution and Investigator with a list of the Study's SAEs (previously received by the Company from the Institution and the Investigator) on a semi-annual basis. Investigator will confirm to Company that all applicable SAEs related to Janssen Product(s) Under Study have been reported to Company.

10.0 Company Responsibilities

Company Representative or designee will provide the Institution and Investigator with the following safety 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.

- ICF risk wording
- any new information, which becomes available during the course of the Study, which may affect the overall safety profile of the Janssen Product(s) Under Study.

11.0 Company Safety Contact Information

Contact details for the Company representative for submission of information required under this exhibit.

SAE/Pregnancy Notifications: IIS-BIO-VIRO-GCO@its.jnj.com
PQC: IIS-BIO-VIRO-GCO@its.jnj.com
Phone: contact the study assigned Janssen Trial Manager
Fax: 1-866-451-0371

12.0 Definitions

12.1 Adverse Event (AE)

Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment administration through 30 days after the last dose of study treatment or study intervention. Any serious adverse event that occurs more than 30 days after the last study treatment and is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 9.2, occurring from the initial study treatment administration through 30 days following the last dose of the study treatment must be recorded as an adverse event in the patient’s source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event.

Any untoward medical event in a patient administered a pharmaceutical product which does not necessarily have to have a causal relationship with the treatment. An adverse event can be any unfavourable and unintended sign (including abnormal finding or lack of expected pharmacological action), symptom, or disease temporarily associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that (investigational or non-investigational) product. This includes any occurrence that is new in onset or aggravated in severity from the baseline condition, or abnormal results of any diagnostic procedures, including laboratory test abnormalities.

12.2 Adverse Event of Special interest

Adverse events of special interest are events that the Company is actively monitoring as a result of a previously identified signal (even if non-serious). Adverse events of special interest of Daratumumab will be reported to the Company as defined in the protocol. In case of any amendments to the AESI list, Company will notify the Institution/Investigator and the Institution/Investigator will inform sites. Institution/Investigator will ensure that these changes are updated in the protocol as soon as practical.

These adverse events are:

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

Sites will revise the AESIs previously entered in the EDC that do not also meet the definition of a SAE to “Acute Adverse Event” instead of “Serious Adverse Event.” Additionally, sites will generate a SAE follow-up report in the EDC for the AESIs that do not meet the definition of a SAE and revise Section D4 of the report to “non-serious” instead of an “important medical event.” No revisions will be made to the AESIs that also meet the definition of a SAE. AESIs previously reported as “non-serious” will be revised in the EDC to “Acute Adverse Event” instead of “Serious Adverse Event.”

12.3 Serious Adverse Event (SAE)

Any adverse event occurring that:

- Results in death;
- Is life-threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Any suspected transmission of any infectious agent via administration of a medicinal product
- Is considered medically significant*

*Any untoward medical occurrence that is considered medically significant. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not result in death, be life-threatening or require hospitalization but may be considered a serious adverse drug experience when, based on appropriate medical judgement, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the bulleted list above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an

emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse or malignancy.

12.4 Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to hospitalization that is the serious event for which details must be provided. Any event requiring hospitalization or prolongation of hospitalization that occurs during a 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 a study. [Note: Hospitalizations that were planned before the signing of ICF 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.]

12.5 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 fulfil the serious adverse event definition.

12.6 Special Situations

The following special situations must be reported to Company with or without an associated serious adverse event (SAE):

- Drug exposure during pregnancy (paternal, maternal)
- Suspected transmission of any infectious agent via administration of a Janssen Product(s) under study.

The following special situations must be reported to the Company when associated with a serious adverse event (SAE):

- Overdose of Janssen Product(s) under study
- Exposure to Janssen Product(s) under study from breastfeeding
- Suspected abuse/misuse of Janssen product(s) under study
- Inadvertent or accidental exposure to Janssen Product(s) under study
- Any failure of expected pharmacological action (i.e., lack of effect) of Janssen Product(s) under study
- Medication error (includes potential, intercepted or actual) involving a Janssen product (with or without patient exposure to the Janssen Product(s) under study, e.g., name confusion)
- Unexpected therapeutic or clinical benefit from use of Janssen Product(s) under study

If no SAE is associated with the special situation, the special situation should be recorded in the CRF and sent annually to the Company.

These safety events may not meet the definition of an adverse event; however, the Parties agree that for reporting purposes, they are deemed to be adverse events.

12.7 Product Quality Complaints

A PQC may have an impact on the safety and efficacy of a Company product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the Company, and are mandated by regulatory agencies worldwide. The Company has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. The Institution agrees that Lot and/or Batch #s

shall be collected, when available, for all PQC reports, including reports of failure of expected pharmacological action (i.e., lack of effect) of a Janssen Medicinal Product. A sample of the suspected product shall be maintained for further investigation if requested by the Company.

Any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or delivery system is considered a PQC. Not all PQCs involve a patient.

Examples of PQC include but are not limited to:

- Mislabeling or misbranding
- Information concerning microbial contamination, including a suspected transmission of any infectious agent by a product
- Any significant chemical, physical, or other changes that indicate deterioration in the distributed product
- Any foreign matter reported to be in the product
- Mixed product, e.g., two drugs are mixed-up in the packaging process
- Incorrect tablet sequence (e.g., oral contraceptive tablets)
- Insecure closure with serious medical consequences, e.g., cytotoxics, child-resistant containers, potent drugs
- Suspected counterfeit or tampered product

- Adverse Device Effects including any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation, installation, operation, or any malfunction of a medical device or combination product. This also includes any event that is a result of a use error or intentional misuse and dosing device malfunctions (e.g. auto-injector button not working, needle detaching from syringe, etc.)
- Physical defect (e.g. abnormal product odor, broken or crushed tablets, etc.)

12.8 "Extraordinary" correspondence

Correspondence with a regulatory authority or ethics committee regarding a safety issue that may impact the safety or benefit-risk balance of the Janssen Product(s) Under Study, and/or may impact patients or public health. Examples include:

- Safety issues relating to a quality defect
- Major safety issues identified with changes in the nature, severity or frequency of known serious adverse reactions which are medically significant or the detection of new risk factors for the development of a known adverse reaction or a new serious adverse reaction.
- Major safety issues identified in the context of ongoing or newly completed post-marketing studies e.g. an unexpected increased rate of fatal or life-threatening adverse events.

12.8.1 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 10.1 for the list of expected adverse events related to the drug under study.

12.9 Adverse Event Characteristics

12.9.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5. A copy of the CTCAE version 5 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

12.9.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

12.10 Serious Adverse Event Reporting Guidelines

12.10.1 Reporting procedures for multi-site trials

All serious adverse events (SAEs) and unanticipated problems (UAPs), regardless of causality to study drug, will be reported to the Sponsor-Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 24 hours of first awareness of the event. Events should be reported using the **Coordinating Center SAE form as available in the study database.** A copy of the **SAE form** should be sent to the Coordinating Center via email to CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event.

Contact information for Sponsor-Investigator SAE Reporting:

Name: Erica Campagnaro, MD
Address: University of Michigan
1500 E Medical Center Dr
Ann Arbor, MI 48109-5848
Telephone: (734) 647-8902
Email: ericacam@med.umich.edu

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All SAEs and UPs will be reported to the IRB per current institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Sponsor-Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug or device. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

12.10.2 Reporting procedures to FDA

In this trial, serious, unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the Food and Drug Administration via the MedWatch 3500A. The Michigan IND/IDE Assistance Program

(MIAP) will be responsible for reporting SAEs to the FDA that meet the reporting requirements in 21 CFR 312.32.
The Multi-site team will coordinate with the Sponsor-Investigator and the Michigan Institute for Clinical and Health Research (MICHR) IND/IDE Investigator Assistance Program (MIAP) office for the reporting of any and all IND safety reports to the FDA as per the requirements outlined in 21 CFR 312.32. A summary of all non-expedited safety reports will be submitted in the annual report.

12.11 Routine Reporting

All other adverse events such as those that are expected or are unlikely or definitely not related to the study participation are to be reported annually as part of regular data submission.

12.12 Reporting of Unanticipated Problems (UAP)

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Another example of a UAP would be a product quality complaint (PQCs). A PQC 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.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

13.0 DRUG INFORMATION

13.1 Daratumumab IV

- Other names:
    - NDC 57894-502-05 contains one 100 mg/5 mL single-dose vial
    - NDC 57894-502-20 contains one 400 mg/20 mL single-dose vial
    - DARZALEX®
- Description: colorless to pale yellow, preservative-free solution for intravenous infusion
- Classification: Immunomodulator (immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody)
- Mode of action: CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including multiple myeloma and other cell types and tissues and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that

binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+Tregs) and B cells (CD38+Bregs) are decreased by daratumumab.

- Pharmacokinetics:
  Over the dose range from 1 to 24 mg/kg as monotherapy or 1 to 16 mg/kg of daratumumab in combination with other treatments, increases in area under the concentration-time curve (AUC) were more than dose-proportional. Following the recommended dose of 16 mg/kg when daratumumab was administered as monotherapy or in combination therapy, the mean serum maximal concentration (Cmax) value at the end of weekly dosing, was approximately 2.7 to 3-fold higher compared to the mean serum Cmax following the first dose. The mean ± standard deviation (SD) trough serum concentration (Cmin) at the end of weekly dosing was 573 ± 332 µg/mL when daratumumab was administered as monotherapy and 502 ± 196 to 607 ± 231 µg/mL when daratumumab was administered as combination therapy. Daratumumab steady state was achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean ± SD ratio of Cmax at steady-state to Cmax after the first dose was 1.6 ± 0.5.
- Pharmacodynamics
  NK cells express CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+CD56dim) NK cells in peripheral whole blood and bone marrow were observed with DARZALEX treatment.

  Distribution
  At the recommended dose of 16 mg/kg, the mean ± SD central volume of distribution was 4.7 ± 1.3 L when daratumumab was administered as monotherapy and 4.4 ± 1.5 L when daratumumab was administered as combination therapy.

  Elimination
  Daratumumab clearance decreased with increasing dose and with multiple dosing. At the recommended dose of 16 mg/kg of daratumumab as monotherapy, the mean ± SD linear clearance was estimated to be 171.4 ± 95.3 mL/day. The mean ± SD estimated terminal half-life associated with linear clearance was 18 ± 9 days when daratumumab administered as monotherapy and 23 ± 12 days when daratumumab was administered as combination therapy.

  Specific Populations
  The following population characteristics have no clinically meaningful effect on the pharmacokinetics of daratumumab in patients administered daratumumab as monotherapy or as combination therapy: sex, age (31 to 84 years), mild [total bilirubin 1 to 1.5 times upper limit of normal (ULN) and any alanine transaminase (ALT)] and moderate (total bilirubin 1.5 to 3 times ULN and any ALT) hepatic impairment, or renal impairment [Creatinine clearance (CLcr) 15 -89 mL/min]. The effect of severe (total bilirubin >3 times ULN and any ALT) hepatic impairment is unknown. Increasing body weight increased the central volume of distribution and clearance of daratumumab, supporting the body weight-based dosing regimen.
- Side effects: The most frequently reported adverse reactions (incidence ≥20%) in clinical trials were: infusion reactions, neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, constipation, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy and upper respiratory tract infection.
- Drug interactions:
  Effect of Other Drugs on Daratumumab

- The coadministration of lenalidomide, pomalidomide or bortezomib with daratumumab did not affect the pharmacokinetics of daratumumab.

Effect of Daratumumab on Other Drugs

- The coadministration of daratumumab with bortezomib did not affect the pharmacokinetics of bortezomib.

- Storage and stability: Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). Do not freeze or shake. Protect from light. Does not contain preservatives.
- Preparation and dispensing: for single use only. Prepare the solution for infusion using aseptic technique as follows:

  - Check that the daratumumab solution is colorless to pale yellow. Do not use if opaque particles, discoloration or other foreign particles are present.
  - Remove a volume of 0.9% Sodium Chloride Injection, USP from the infusion bag/container that is equal to the required volume of daratumumab solution.
  - Withdraw the necessary amount of daratumumab solution and dilute to the appropriate volume by adding to the infusion bag/container containing 0.9% Sodium Chloride Injection, USP. Infusion bags/containers must be made of either polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) orpolyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
  - Gently invert the bag/container to mix the solution. Do not shake.
  - Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein.
  - Do not use if visibly opaque particles, discoloration or foreign particles are observed.
- Administration:
  Refer to Section 5.1

  - Since daratumumab does not contain a preservative, administer the diluted solution immediately at room temperature 15°C–25°C (59°F–77°F) and in room light. Diluted solution may be kept at room temperature for a maximum of 15 hours (including infusion time).
  - If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions 2°C – 8°C (36°F–46°F) and protected from light. Do not freeze.
- Availability: The investigator or designee will order drug from Janssen (or 3rd party vendor), according to the ordering instructions provided by Coordinating Center.
- Return and retention of drug the investigator will be instructed by the Coordinating Center on the return or destruction of unused daratumumab. If any daratumumab is lost or damaged, its disposition should be documented in the source documents. Daratumumab supplies will be retained at the clinical site pending instructions for disposition by the Coordinating Center.

  If instructed to do so, empty vials and unused supplies of daratumumab should be destroyed according to institutional policies. Destruction will be documented in the drug accountability forms.
- Drug accountability: The investigator or designee is responsible for taking an inventory of each shipment of daratumumab received and comparing it with the accompanying accountability form. The Investigator, or responsible party designated by the investigator, will verify the accuracy of the information on the form, sign and date it, and retain a copy in the study file. Accurate records will be kept in the source documentation of all drug administration (including dispensing and dosing).

13.2 Daratumumab SQ

Information is taken from DARZALEX FASPRO (daratumumab and hyaluronidase-fihj) package insert. Horsham, PA: Janssen Biotech, Inc.; 2021 Mar.

- Other names:
  - NDC 57894-503-01 contains 1,800 mg of daratumumab and 30,000 units of hyaluronidase per 15 mL single-dose vial
  - DARZALEX FASPRO ®

- Description: sterile, preservative-free, colorless to yellow, and clear to opalescent solution for subcutaneous use supplied as individually packaged single-dose vials.

- Classification: Immunomodulator (immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody).

- Mode of action: CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including clonal plasma cells in multiple myeloma and light chain (AL) amyloidosis, as well as other cell types. Surface CD38 has multiple functions, including receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1. human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+Tregs) and B cells (CD38+Bregs) are decreased by daratumumab.
  Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. In the doses administered, hyaluronidase in DARZALEX FASPRO acts locally. The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

- Pharmacokinetics: Following the recommended dose of DARZALEX FASPRO 1,800 mg/30,000 units, Cmax increased 4.8-fold and AUC0-7 days increased 5.4-fold from the 1st dose to the 8th dose. Additional information daratumumab exposure is provide in Section 12.3 the drug label.

  <u>Absorption</u>
  At the recommended dose of DARZALEX FASPRO 1,800 mg/30,000 units, the absolute bioavailability is 69%, with peak concentrations occurring around 3 days (Tmax) in patients with multiple myeloma.

  <u>Distribution</u>
  The estimated mean (coefficient of variation, CV) volume of distribution for the central compartment is 5.2 L (37%) and peripheral compartment was 3.8 L in patients with multiple myeloma.

  <u>Elimination</u>
  Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. The estimated mean (CV%) linear clearance of daratumumab is 119 mL/day

(59%) in patients with multiple myeloma. The estimated mean (CV%) elimination half-life associated with linear clearance is 20 days (22%) in patients with multiple myeloma.

Specific Populations
The following population characteristics have no clinically meaningful effect on the pharmacokinetics of daratumumab in patients administered DARZALEX FASPRO as monotherapy or as combination therapy: sex, age (33 to 92 years), renal impairment [Creatinine clearance (CLcr) 15 to 89 mL/min as determined by the Cockcroft-Gault formula], and mild hepatic impairment (total bilirubin 1 to 1.5 times ULN and AST>ULN). The effect of moderate and severe hepatic impairment on daratumumab pharmacokinetics is unknown.

Racial or Ethnic Groups
Of 190 patients with light chain (AL) amyloidosis who received DARZALEX FASPRO and had a maximum C_{trough} after the 8th dose, African-Americans (4%) had 24% higher daratumumab mean maximum Ctrough after the 8th dose compared to that of Whites (83%) and Asians (10%) had 16% higher mean maximum C_{trough} after the 8th dose compared to that of Whites. The difference in exposure between that of Asians and Whites could be explained in part by differences in body size. The effect of African-American race on exposure and related safety and efficacy of daratumumab is unknown.

Body Weight
In patients with multiple myeloma who received DARZALEX FASPRO 1,800 mg/30,000 units as monotherapy, the mean maximum C_{trough} after the 8th dose was 12% lower in the higher body weight (BW) group (>85 kg), while the mean maximum C_{trough} after the 8th dose was 81% higher in the lower BW group (=50 kg) compared to the corresponding BW groups in the intravenous daratumumab arm.

- Pharmacodynamics: NK cells express CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+CD56dim) NK cells in peripheral whole blood and bone marrow were observed with DARZALEX FASPRO treatment.

- Side effects: The most common adverse reactions (=20%) in patients with multiple myeloma who received daratumumab in combination with lenalidomide and dexamethasone are fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia and dyspnea.
  The most common adverse reaction (≥20%) in patients with multiple myeloma who received DARZALEX FASPRO monotherapy is upper respiratory tracts infection.
  The most common (=40%) hematology laboratory abnormalities with DARZALEX FASPRO are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

- Drug interactions: See the daratumumab IV section above.

- Storage and stability: Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF) in the original carton to protect from light. Do not freeze or shake.

- Preparation and dispensing:
  DARZALEX FASPRO is ready to use.
  To prevent medication errors, check the vial labels to ensure that the drug being prepared is DARZALEX FASPRO for subcutaneous use.

  - Remove the DARZALEX FASPRO vial from refrigerated storage [2°C to 8°C (36°F to 46°F)] and equilibrate to ambient temperature [15°C to 30°C (59°F to 86°F)]. Store the

unpunctured vial at ambient temperature and ambient light for a maximum of 24 hours. Keep out of direct sunlight. Do not shake.
  - Withdraw 15 mL (1800mg of daratumumab) from the vial into a syringe.
  - DARZALEX FASPRO is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles. Use the product immediately.
  - After the solution of DARZALEX FASPRO is withdrawn into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe appropriately to include the route of administration per institutional standards.
  - To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.
  - Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if opaque particles, discoloration or other foreign particles are present.

- Administration:
  Refer to Section 5.1.8

  - DARZALEX FASPRO should be administered by a healthcare provider.
  - To prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is DARZALEX FASPRO for subcutaneous use. Do not administer DARZALEX FASPRO intravenously.
  - If the syringe containing DARZALEX FASPRO is not used immediately, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours and/or at room temperature at 15°C to 25°C (59°F to 77°F) for up to 12 hours under ambient light.
    - Discard if storage time exceeds these limits.
    - If stored in the refrigerator, allow the solution to come to room temperature before administration.

- Availability: The investigator or designee will order drug from Janssen (or 3rd party vendor), according to the ordering instructions provided by Coordinating Center.

- Return and retention of drug the investigator will be instructed by the Coordinating Center on the return or destruction of unused DARZALEX FASPRO vials. If any vial is lost or damaged, its disposition should be documented in the source documents. DARZALEX FASPRO supplies will be retained at the clinical site pending instructions for disposition by the Coordinating Center.

  If instructed to do so, empty bottles and unused supplies of DARZALEX FASPRO should be destroyed according to institutional policies. Destruction will be documented in the drug accountability forms.

Drug accountability: The investigator or designee is responsible for taking an inventory of each shipment of DARZALEX FASPRO received and comparing it with the accompanying accountability form. The Investigator, or responsible party designated by the investigator, will verify the accuracy of the information on the form, sign and date it, and retain a copy in the study file. Accurate records will be kept in the source documentation of all drug administration (including dispensing and dosing).

13.3 Lenalidomide

- Other names: Lenalidomide (REVLIMID®)

- Description: a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2**H**-isoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3.
- Classification: immunomodulatory agent
- Mode of action: The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and anti-angiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.
- Pharmacokinetics:
  Absorption: Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.
  In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.
  Distribution: In vitro (14C)-lenalidomide binding to plasma proteins is approximately 30%.
  Metabolism and Excretion: The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.
    - Side effects: The most common side effects are neutropenia and thrombocytopenia.
    - Drug interactions: None
    - Storage and stability: At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Lenalidomide should be stored according to manufacturer instructions reported on labels and storage temperature should not exceed 25°C.
- Preparation and dispensing: per commercial
- Administration:
  Refer to Section 5.1
- Availability: Lenalidomide is commercially available and therefore is to be purchased by a third party. This drug will not be supplied by the study.
- Return and retention of drug: per institutional policies.
- Drug accountability: per institutional policies.

13.4 Bortezomib

- Other names for the drug: VELCADE ®, NDC 63020-049-01
- Description: single-use 10 mL vial contains 3.5 mg of bortezomib as lyophilized powder.
- Classification - type of agent: proteasome inhibitor
- Mode of action: Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin proteasome pathway plays an essential role in

regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma.

- Pharmacokinetics:
  Following intravenous administration of 1 mg/m^2 and 1.3 mg/m^2 doses to 24 patients with multiple myeloma (n=12, per each dose level), the mean maximum plasma concentrations of bortezomib (Cmax) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m^2 dose and 76 to 108 hours after the 1.3mg/m^2 dose. The mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m^2, respectively. Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m^2 dose to patients (n = 14 for intravenous, n = 17 for subcutaneous) with multiple myeloma, the total systemic exposure after repeat dose administration (AUClast) was equivalent for subcutaneous and intravenous administration. The Cmax after subcutaneous administration (20.4 ng/mL) was lower than intravenous (223 ng/mL). The AUClast geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% - 122.80%.

  Distribution: The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

  Metabolism: In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

  Elimination: The pathways of elimination of bortezomib have not been characterized in humans.
- Side effects: Most commonly reported adverse reactions (incidence ≥ 20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia. Please see FDA package insert for a comprehensive list of adverse events.
- Drug Interactions:

CYP3A4 inhibitors (ketoconazole, ritonavir): co-administration of ketoconazole increased the exposure of bortezomib by 35% in 12 patients. Patients receiving strong CYP3A4 inhibitors should be monitored for signs of bortezomib toxicity and considered for a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors.

CYP3A4 inducers: co-administration of rifampin is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur.

Efficacy may be reduced when bortezomib is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers should not be used in patients receiving bortezomib. St. John's Wort (*Hypericum perforatum*) may decrease bortezomib exposure unpredictably and should be avoided. Patients will have to switch from strong CYP3A4 inducers to alternative agents at time of bortezomib administration.

- Storage and stability: Unopened vials may be stored at controlled room temperature 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF) [see USP Controlled Room Temperature]. Retain in original package to protect from light. Follow guidelines for handling and disposal for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact.

  Unopened vials of VELCADE are stable until the date indicated on the package when stored in the original package protected from light. VELCADE contains no antimicrobial preservative. Reconstituted VELCADE should be administered within 8 hours of preparation. When reconstituted as directed, VELCADE may be stored at 25ºC (77ºF). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to 8 hours in a syringe; however, total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

- Preparation and Dispensing:
  Reconstitute only with 0.9% sodium chloride. The reconstituted product should be a clear and colorless solution.

  Different volumes of 0.9% sodium chloride are used to reconstitute the product for the different routes of administration. The reconstituted concentration of bortezomib for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL). Because of this, caution should be used when calculating the volume to be administered.

  For each 3.5 mg single-use vial of bortezomib, reconstitute with 1.4 mL of 0.9% sodium chloride for a final bortezomib concentration of 2.5 mg/mL to be administered subcutaneously.

  After determining the patient body surface area (BSA) in square meters, use the following equation to calculate the total volume (mL) of reconstituted bortezomib to be administered:

  Subcutaneous administration [2.5 mg/mL concentration]

$$\frac{\text{Bortezomib dose } \left(\frac{\text{mg}}{m^2}\right) \text{x patient BSA } (m^2)}{2.5 \text{ mg/mL}} = \text{Total bortezomib volume (mL) to be administered}$$

- Administration:
  Refer to Section 5.1

  The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose. When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated. If local injection site reactions occur following bortezomib administration subcutaneously, a less concentrated bortezomib solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. Alternatively, the intravenous route of administration should be considered. Bortezomib is an antineoplastic. Procedures for proper handling and disposal should be considered.

Stickers that indicate the route of administration are provided with each bortezomib vial. These stickers should be placed directly on the syringe of bortezomib once bortezomib is prepared to help alert practitioners of the correct route of administration for bortezomib.

As administration will be directly administered by clinical personnel, adherence will be directly observed and documented accordingly.

- Availability: Bortezomib is commercially available and therefore is to be purchased by a third party. This drug will not be supplied by the study.
- Return and retention of drug: per institutional policies.
- Drug accountability: per institutional policies.

13.5 Dexamethasone

- Other names: Decadron (NSC-34521)
- Description: Dexamethasone (Decadron) is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11b, 17, 21-trihydroxy-16a-methyl-pregna-1, 4-diene-3, 20-dione.
- Classification: adrenocortical steroid
- Mode of action: Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.
- Pharmacokinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Dexamethasone is insoluble in water. Glucocorticoids have salt-retaining properties, although dexamethasone nearly completely lacks this property. Dexamethasone may suppress the body's response to viral and bacterial infections. Equivalent doses are as follows:

Dexamethasone	Methyl-prednisolone and Triamcinolone	Prednisolone and Prednisone	Hydrocortisone	Cortisone
0.75 mg	4 mg	5 mg	20 mg	25 mg

- Side effects: Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

  Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.
- Drug interactions: None
- Storage and stability: Dexamethasone is to be stored at room temperature.

- Preparation and dispensing: Dexamethasone is available in seven potencies (0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg) tablet form.
- Administration:
  Refer to Section 5.1
  - Availability: Dexamethasone is commercially available and therefore is to be purchased by a third party. This drug will not be supplied by the study.
  - Return and retention of drug: per institutional policies.
  - Drug accountability: per institutional policies.

14.0 CORRELATIVES/SPECIAL STUDIES

14.1 Sample Collection Guidelines

Bone marrow, peripheral blood and stool samples (optional) are to be collected according to section 6.2 Time and Events Table and the Lab Manual.

14.1.1 Collection

The blood, stool, and bone marrow collections are to occur at the time of those performed for clinical assessments. All specimens are to be delivered to the University of Michigan Lab as outlined in the Lab Manual.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

14.2 Assay Methodology Laboratory Research Studies

14.2.1 Bone marrow MRD testing by Next Generation Sequencing (NGS)

NGS MRD will be performed by Adaptive Technologies, as approved by FDA and covered by Medicare.

14.3 Correlative Studies

14.3.1 Immune Profiling (IP)

The interaction between myeloma cells and microenvironment takes place within a complex system. Myeloma cells undergo phenotypic shifts during disease evolution as well as in response to therapy, creating dynamic immunophenotypic patterns. There is growing interest in incorporating immune profiling into clinical trial designs (Holstein, Avet-Loiseau et al. 2018). It is valuable to determine whether specific immunophenotypic repertoire in both bone marrow microenvironment and peripheral blood can be correlated with the MRD status and treatment outcomes. Most myeloma patients will inevitably relapse, so identifying the favorable immune profile patterns in patients who have prolonged remission will facilitate the early identification of such patients as well as development of novel strategies for better disease control in patients with unfavorable immune profile patterns.

Daratumumab is a human IgG1 kappa monoclonal antibody, which binds to CD38-expressing myeloma cells and induces tumor cell death through multiple immune mediated mechanisms. Furthermore, it also depletes CD 38+ regulatory cells including T regs, B regs, and MDSC and promotes clonal expansion of cytotoxic T cell population, suggesting an immunomodulatory role in the therapy (Krejcik, Casneuf et al. 2016).

Additional correlative studies are being planned for immunology and metabolomics and microbiome.

14.3.2 Imaging Studies with PET/CT

Imaging MRD is now included in IMWG and NCCN response criteria (Anderson 2016, Kumar, Paiva et al. 2016). There was data showing MRD negative patients continue to relapse, probably due to residual disease at sites other than the one commonly investigated for MRD, the posterior iliac crest. It is therefore important to include functional imaging such as PET/CT to complement MRD data, especially in this study with MRD-driven therapeutic decision (Cavo, Terpos et al. 2017).

PET/CT will be performed at time points per section 6.2 Time and Events Table. If not approved by insurance, MRI can be considered.

14.3.3 Patient Reported Outcomes

To measure peripheral neuropathy, the FACT/GOG-Ntx neurological instrument will be used (Richardson, Briemberg et al. 2006). To measure functional status, well-being, and symptoms, the EQ-5D-5L instrument will be used (EuroQolGroup 1990, Herdman, Gudex et al. 2011). These questionnaires will be completed at the time points outlined in the TIME AND EVENTS SCHEDULE before any other study procedures scheduled for the same day.

14.4 Specimen Banking

Patient samples collected for this study will be retained at the University of Michigan Laboratory. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

PI will be responsible for reviewing and approving requests for clinical specimens from potential research collaborators outside of the University of Michigan. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of a clinical specimen will be the property of the University of Michigan for publication, and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by the University of Michigan, the investigator or a collaborating researcher or entity.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories.

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design/Study Endpoints

This is a prospective, single-arm trial evaluating the efficacy of an MRD-based decision-making strategy with upfront daratumumab-based therapy. As described in 2.4, the primary endpoint will be achieving MRD-negativity after six cycles of induction followed by three cycles of consolidation therapy. We will seek to establish evidence that the true proportion of patients who can achieve MRD negativity after induction + consolidation (if still MRD+ after induction) is high, which we define as any response rate that is at least 23%.

15.2 Sample Size and Accrual

We will enroll 50 evaluable patients. We will conduct a two-stage design, with an interim futility analysis after the primary endpoint is available on the first 20 evaluable enrolled patients. We will proceed to a final analysis with all 50 evaluable patients if at least 2/20 (10%) of patients achieve MRD negativity after consolidation. This is not a typical 'optimal' or 'minimax' two-stage design. Rather, the interim analysis is intentionally more anti-conservative than these designs so as to increase the probability that we will know that the interim analysis has been successfully passed prior to actually having measured response on all 20 initial evaluable patients. The end of 11.2 describes this rationale in more detail.

If the enrolled patient does not have MRD tests completed (including clonal ID at baseline, MRD1 and MRD2), patient will be considered as non-evaluable for purposes of the primary endpoint and secondary endpoints 2.5.3 and 2.5.4.

If the enrolled patient comes off study, whether or not the patient is evaluable versus non-evaluable will be based on the unanimous consensus from the committee composed by the Sponsor-Investigator, treating physician, and statistician. If Sponsor-Investigator is the treating physician, an independent physician will be included to determine whether or not that specific patient is evaluable. This is to ensure that investigators are not taking the patient off the study for the potential bias of avoiding MRD tests when MRD positivity is anticipated.

Non-evaluable patients will be excluded from the primary analysis and secondary analyses 12.3.2.3 and 12.3.2.4.

If we do proceed to the final analysis, then we will declare the trial outcome to be a success if at least 9/50 patients (18%) achieve MRD negativity. The below table gives the proportions (to 2 digits) of outcomes for this design under different proportions of true MRD negativity.

Table 12.2-1: Operating characteristics of our design under different true proportions who achieve MRD-negativity. The sum of the second and third columns denote the probability of the trial stopping unsuccessfully, and the fourth column denotes the probability of the trial declaring success.

True proportion achieving MRD-negativity	% stop at interim futility analysis	% proceed to final analysis and fail	% proceed to final analysis and succeed
5%	74%	26%	<1%
10%	39%	55%	5.5%
15%	18%	50%	32%
20%	6.9%	25%	68%
21%	5.7%	21%	74%
22%	4.6%	17%	79%
23%	3.7%	13%	83%
24%	3.0%	10%	87%
25%	2.4%	7.9%	90%

30%	<1%	1.6%	98%
35%	<1%	<1%	>99%

Defining the 'null' set of scenarios as all rates less than or equal to 10%, the one-sided type I error of this design is no greater than 5.5%; defining the 'non-null' set of scenarios as all rates greater than at least 23%, the power of this design is no smaller than 83%. The power quickly increases beyond 83% when the true MRD-negativity rate increases. We will also report confidence intervals for estimated proportions based upon inverted score tests.

We anticipate enrolling patients at a rate of 1.33 to 1.5 patients/month. Thus, the entire accrual period will require approximately 3 years, with an additional up-to 24 + 12 weeks beyond enrollment of the final patient (induction + consolidation) for the primary endpoint to be observed. A pause in patient enrollment may be required at the time of the interim futility analysis if the decision to stop is not immediately evident. Should the decision be made to pause enrollment, it will be communicated to participating sites. Such a pause is undesirable given that the primary endpoint requires 24 or 36 weeks of follow-up, and so we have intentionally designed the interim futility analysis to be anti-conservative. That is, assuming the rate of MRD-negativity is non-null, i.e. > 22%, we will know that we have successfully passed the interim futility analysis after the first 10 patients' primary endpoint is observed with probability 71%, i.e. the probability of observing 2 or more MRD negative patients among the first 10 enrolled is 71%. Assuming that the first 10 patients have their endpoint observed at approximately the same time as the first 20 patients are enrolled, this will minimize the time that enrollment is paused.

15.3 Data Analyses Plans

15.3.1 Primary Analysis

We will report the total proportion of patients achieving the primary endpoint of MRD-negativity after induction or, if necessary, consolidation. Confidence limits derived from the Wilson score interval will be reported.

15.3.2 Secondary Analyses

15.3.2.1 We will graphically and numerically estimate OS using Kaplan-Meier methodology, administratively censoring those patients who are alive at the last follow-up date. Confidence limits will also be included.

15.3.2.2 We will graphically and numerically estimate PFS using Kaplan-Meier methodology, administratively censoring those patients who are alive and free

of disease progression at the last follow-up date. Confidence limits will also be included.

15.3.2.3 We will report the proportion of patients who were not MRD-negative after induction and subsequently achieve MRD-negativity after consolidation. Confidence limits derived from the Wilson score interval will be reported.

15.3.2.4 We will summarize the proportions of those patients who maintain MRD-negativity across different time points.

15.3.2.5 Health-related quality of life and neurotoxicity assessment changes from baseline using FACT/GOG-Neurotoxicity questionnaire and EQ-5D will be characterized using descriptive statistics.

15.3.2.6 Incidence of treatment-emergent AEs will be summarized in a tabular format by MedDRA coded terms.

15.3.2.7 Report the total proportion of patients with a successful stem cell mobilization after receiving Dara-based induction therapy. Confidence limits derived from the Wilson score interval will be reported.

15.3.3 Exploratory Analysis

15.3.3.1 We will quantify agreement on MRD classification between NGS and imaging using Cohen's kappa or other suitable measures of inter-rater agreement.

15.3.3.2 We will quantify the extent to which MRD classification via NGS correlates with changes in APC, ILC/NK and T-cell subsets and subsequent functional studies using two-sample Wilcoxon tests (with MRD classification status as the grouping variable).

15.3.3.3 We will describe the MRD results and clinical outcome in patients with baseline high risk cytogenetic features.

16.0 DATA AND SAFETY MONITORING

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

The Sponsor-Investigator (S-I)/Study Principal Investigator will provide ongoing monitoring of data and patient safety in this trial and conduct regular data review with participating sites.

The Sponsor-Investigator (S-I)/Study Principal Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites per a defined quarterly meeting cadence. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (SAE reporting, unanticipated problems)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Sponsor-Investigator (S-I)/Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a quarterly basis for independent review.

17.0 QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

18.0 CLINICAL MONITORING PROCEDURES

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of the University of Michigan Rogel Cancer Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo a site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting can occur after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and study staff should make every effort in attending the site initiation meeting. Study-related questions or issues identified during the site initiation meeting will be followed-up by the appropriate University of Michigan Rogel Cancer Center personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes Cycle 2 of treatment. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit if all of the following apply:

- No patient has signed the Informed Consent Form and has enrolled into the study.
- Investigational agent has not been dispensed.
- All investigational agent and materials have been returned as defined for the study or destroyed and accounted for properly.

19.0 DATA MANAGEMENT

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based Velos data management system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration
    - Subject entry into Velos
        - Subject Status
        - Demographics
- During study participation

All data should be entered online within 10 business days of data acquisition. Information on dose limiting toxicity events must be entered within one business day. Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 9.5 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

REFERENCES

Anderson, K. C. (2016). "NCCN Guidelines Update for Multiple Myeloma." J Natl Compr Canc Netw **14**(5 Suppl): 675-677.
Barr, H., J. Dempsey, A. Waller, Y. Huang, N. Williams, N. Sharma, D. M. Benson, A. E. Rosko, Y. A. Efebera and C. C. Hofmeister (2018). "Ninety-minute daratumumab infusion is safe in multiple myeloma." Leukemia **32**(11): 2495-2518.
Cavo, M., E. Terpos, C. Nanni, P. Moreau, S. Lentzsch, S. Zweegman, J. Hillengass, M. Engelhardt, S. Z. Usmani, D. H. Vesole, J. San-Miguel, S. K. Kumar, P. G. Richardson, J. R. Mikhael, F. L. da Costa, M. A. Dimopoulos, C. Zingaretti, N. Abildgaard, H. Goldschmidt, R. Z. Orlowski, W. J. Chng, H. Einsele, S. Lonial, B. Barlogie, K. C. Anderson, S. V. Rajkumar, B. G. M. Durie and E. Zamagni (2017). "Role of 18F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group." Lancet Oncol **18**(4): e206-e217.
Chapuy, C. I., R. T. Nicholson, M. D. Aguad, B. Chapuy, J. P. Laubach, P. G. Richardson, P. Doshi and R. M. Kaufman (2015). "Resolving the daratumumab interference with blood compatibility testing." Transfusion **55**(6 Pt 2): 1545-1554.
Corral, L. G., P. A. Haslett, G. W. Muller, R. Chen, L. M. Wong, C. J. Ocampo, R. T. Patterson, D. I. Stirling and G. Kaplan (1999). "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha." J Immunol **163**(1): 380-386.
Costello, C. (2017). "An update on the role of daratumumab in the treatment of multiple myeloma." Ther Adv Hematol **8**(1): 28-37.
Davies, F. E., N. Raje, T. Hideshima, S. Lentzsch, G. Young, Y. T. Tai, B. Lin, K. Podar, D. Gupta, D. Chauhan, S. P. Treon, P. G. Richardson, R. L. Schlossman, G. J. Morgan, G. W. Muller, D. I. Stirling and K. C. Anderson (2001). "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma." Blood **98**(1): 210-216.
Dimopoulos, M., A. Spencer, M. Attal, H. M. Prince, J. L. Harousseau, A. Dmoszynska, J. San Miguel, A. Hellmann, T. Facon, R. Foa, A. Corso, Z. Masliak, M. Olesnyckyj, Z. Yu, J. Patin, J. B. Zeldis, R. D. Knight and I. Multiple Myeloma Study (2007). "Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma." N Engl J Med **357**(21): 2123-2132.
Dimopoulos, M. A., A. Oriol, H. Nahi, J. San-Miguel, N. J. Bahlis, S. Z. Usmani, N. Rabin, R. Z. Orlowski, M. Komarnicki, K. Suzuki, T. Plesner, S. S. Yoon, D. Ben Yehuda, P. G. Richardson, H. Goldschmidt, D. Reece, S. Lisby, N. Z. Khokhar, L. O'Rourke, C. Chiu, X. Qin, M. Guckert, T. Ahmadi, P. Moreau and P. Investigators (2016). "Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma." N Engl J Med **375**(14): 1319-1331.
Dredge, K., R. Horsfall, S. P. Robinson, L. H. Zhang, L. Lu, Y. Tang, M. A. Shirley, G. Muller, P. Schafer, D. Stirling, A. G. Dalgleish and J. B. Bartlett (2005). "Orally administered lenalidomide (CC-5013) is anti-angiogenic in vivo and inhibits endothelial cell migration and Akt phosphorylation in vitro." Microvasc Res **69**(1-2): 56-63.
Durie, B. G. and S. E. Salmon (1975). "A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival." Cancer **36**(3): 842-854.
EuroQolGroup (1990). "EuroQol--a new facility for the measurement of health-related quality of life." Health Policy **16**(3): 199-208.
Gormley, N. J., A. T. Farrell and R. Pazdur (2016). "Minimal Residual Disease as a Potential Surrogate End Point-Lingering Questions." JAMA Oncol.
Gormley, N. J., D. M. Turley, J. S. Dickey, A. T. Farrell, G. H. Reaman, E. Stafford, L. Carrington and G. E. Marti (2016). "Regulatory perspective on minimal residual disease flow cytometry testing in multiple myeloma." Cytometry B Clin Cytom **90**(1): 73-80.
Greipp, P. R., J. San Miguel, B. G. Durie, J. J. Crowley, B. Barlogie, J. Blade, M. Boccadoro, J. A. Child, H. Avet-Loiseau, R. A. Kyle, J. J. Lahuerta, H. Ludwig, G. Morgan, R. Powles, K. Shimizu, C. Shustik, P. Sonneveld, P. Tosi, I. Turesson and J. Westin (2005). "International staging system for multiple myeloma." J Clin Oncol **23**(15): 3412-3420.
Harousseau, J. L. and H. Avet-Loiseau (2017). "Minimal Residual Disease Negativity Is a New End Point of Myeloma Therapy." J Clin Oncol **35**(25): 2863-2865.

Herdman, M., C. Gudex, A. Lloyd, M. Janssen, P. Kind, D. Parkin, G. Bonsel and X. Badia (2011). "Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L)." Qual Life Res **20**(10): 1727-1736.
Hideshima, T., D. Chauhan, Y. Shima, N. Raje, F. E. Davies, Y. T. Tai, S. P. Treon, B. Lin, R. L. Schlossman, P. Richardson, G. Muller, D. I. Stirling and K. C. Anderson (2000). "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy." Blood **96**(9): 2943-2950.
Holstein, S. A., H. Avet-Loiseau, T. Hahn, C. M. Ho, J. G. Lohr, N. C. Munshi, B. Paiva, M. C. Pasquini, J. D. Tario, S. Z. Usmani, P. K. Wallace, K. Weisel and P. L. McCarthy (2018). "BMT CTN Myeloma Intergroup Workshop on Minimal Residual Disease and Immune Profiling: Summary and Recommendations from the Organizing Committee." Biol Blood Marrow Transplant **24**(4): 641-648.
Krejcik, J., T. Casneuf, I. S. Nijhof, B. Verbist, J. Bald, T. Plesner, K. Syed, K. Liu, N. W. van de Donk, B. M. Weiss, T. Ahmadi, H. M. Lokhorst, T. Mutis and A. K. Sasser (2016). "Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma." Blood **128**(3): 384-394.
Kumar, S., B. Paiva, K. C. Anderson, B. Durie, O. Landgren, P. Moreau, N. Munshi, S. Lonial, J. Blade, M. V. Mateos, M. Dimopoulos, E. Kastritis, M. Boccadoro, R. Orlowski, H. Goldschmidt, A. Spencer, J. Hou, W. J. Chng, S. Z. Usmani, E. Zamagni, K. Shimizu, S. Jagannath, H. E. Johnsen, E. Terpos, A. Reiman, R. A. Kyle, P. Sonneveld, P. G. Richardson, P. McCarthy, H. Ludwig, W. Chen, M. Cavo, J. L. Harousseau, S. Lentzsch, J. Hillengass, A. Palumbo, A. Orfao, S. V. Rajkumar, J. San Miguel and H. Avet-Loiseau (2016). "International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma." Lancet Oncol **17**(8): e328-346.
Landgren, O. and S. Giralt (2016). "MRD-driven treatment paradigm for newly diagnosed transplant eligible multiple myeloma patients." Bone Marrow Transplant.
Landgren, O. and E. H. Rustad (2019). "Meeting report: Advances in minimal residual disease testing in multiple myeloma 2018." ADVANCES IN CELL AND GENE THERAPY **2**(1): e26.
Laubach, J., L. Garderet, A. Mahindra, G. Gahrton, J. Caers, O. Sezer, P. Voorhees, X. Leleu, H. E. Johnsen, M. Streetly, A. Jurczyszyn, H. Ludwig, U. H. Mellqvist, W. J. Chng, L. Pilarski, H. Einsele, J. Hou, I. Turesson, E. Zamagni, C. S. Chim, A. Mazumder, J. Westin, J. Lu, T. Reiman, S. Kristinsson, D. Joshua, M. Roussel, P. O'Gorman, E. Terpos, P. McCarthy, M. Dimopoulos, P. Moreau, R. Z. Orlowski, J. S. Miguel, K. C. Anderson, A. Palumbo, S. Kumar, V. Rajkumar, B. Durie and P. G. Richardson (2016). "Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group." Leukemia **30**(5): 1005-1017.
Lokhorst, H. M., T. Plesner, J. P. Laubach, H. Nahi, P. Gimsing, M. Hansson, M. C. Minnema, U. Lassen, J. Krejcik, A. Palumbo, N. W. van de Donk, T. Ahmadi, I. Khan, C. M. Uhlar, J. Wang, A. K. Sasser, N. Losic, S. Lisby, L. Basse, N. Brun and P. G. Richardson (2015). "Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma." N Engl J Med **373**(13): 1207-1219.
Lonial, S., B. M. Weiss, S. Z. Usmani, S. Singhal, A. Chari, N. J. Bahlis, A. Belch, A. Krishnan, R. A. Vescio, M. V. Mateos, A. Mazumder, R. Z. Orlowski, H. J. Sutherland, J. Bladé, E. C. Scott, A. Oriol, J. Berdeja, M. Gharibo, D. A. Stevens, R. LeBlanc, M. Sebag, N. Callander, A. Jakubowiak, D. White, J. de la Rubia, P. G. Richardson, S. Lisby, H. Feng, C. M. Uhlar, I. Khan, T. Ahmadi and P. M. Voorhees (2016). "Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial." Lancet **387**(10027): 1551-1560.
Mateos, M. V., M. A. Dimopoulos, M. Cavo, K. Suzuki, A. Jakubowiak, S. Knop, C. Doyen, P. Lucio, Z. Nagy, P. Kaplan, L. Pour, M. Cook, S. Grosicki, A. Crepaldi, A. M. Liberati, P. Campbell, T. Shelekhova, S. S. Yoon, G. Iosava, T. Fujisaki, M. Garg, C. Chiu, J. Wang, R. Carson, W. Crist, W. Deraedt, H. Nguyen, M. Qi and J. San-Miguel (2018). "Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma." N Engl J Med **378**(6): 518-528.
Munshi, N. C., H. Avet-Loiseau, A. C. Rawstron, R. G. Owen, J. A. Child, A. Thakurta, P. Sherrington, M. K. Samur, A. Georgieva, K. C. Anderson and W. M. Gregory (2016). "Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-analysis." JAMA Oncol.
Paiva, B., M. T. Cedena, N. Puig, P. Arana, M. B. Vidriales, L. Cordon, J. Flores-Montero, N. C. Gutierrez, M. L. Martin-Ramos, J. Martinez-Lopez, E. M. Ocio, M. T. Hernandez, A. I. Teruel, L. Rosinol, M. A. Echeveste, R. Martinez, M. Gironella, A. Oriol, C. Cabrera, J. Martin, J. Bargay, C. Encinas, Y. Gonzalez, J. J. Van Dongen, A. Orfao, J. Blade, M. V. Mateos, J. J. Lahuerta and J. F. San Miguel (2016). "Minimal

residual disease monitoring and immune profiling in multiple myeloma in elderly patients." Blood **127**(25): 3165-3174.
Paiva, B., N. C. Gutierrez, L. Rosinol, M. B. Vidriales, M. A. Montalban, J. Martinez-Lopez, M. V. Mateos, M. T. Cibeira, L. Cordon, A. Oriol, M. J. Terol, M. A. Echeveste, R. de Paz, F. de Arriba, L. Palomera, J. de la Rubia, J. Diaz-Mediavilla, A. Sureda, A. Gorosquieta, A. Alegre, A. Martin, M. T. Hernandez, J. J. Lahuerta, J. Blade and J. F. San Miguel (2012). "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 **119**(3): 687-691.
Palumbo, A., A. Chanan-Khan, K. Weisel, A. K. Nooka, T. Masszi, M. Beksac, I. Spicka, V. Hungria, M. Munder, M. V. Mateos, T. M. Mark, M. Qi, J. Schecter, H. Amin, X. Qin, W. Deraedt, T. Ahmadi, A. Spencer, P. Sonneveld and C. Investigators (2016). "Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma." N Engl J Med **375**(8): 754-766.
Palumbo, A., S. V. Rajkumar, J. F. San Miguel, A. Larocca, R. Niesvizky, G. Morgan, O. Landgren, R. Hajek, H. Einsele, K. C. Anderson, M. A. Dimopoulos, P. G. Richardson, M. Cavo, A. Spencer, A. K. Stewart, K. Shimizu, S. Lonial, P. Sonneveld, B. G. Durie, P. Moreau and R. Z. Orlowski (2014). "International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation." J Clin Oncol **32**(6): 587-600.
Plesner, T., Arkenau, H, Gimsing P, Jakub K, Lemech C, Minnema M, Lassen U, Laubach JP, Palumbo A, Lisby S, Basse L, Wang J, Sasser AK, Guckert ME, de Boer C, Khokhar NZ, Yeh H, Clemens PL, Ahmadi T, Lokhorst HM, and Richardson PG (2016). "Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma." Blood **128**(14): 1821-1828.
Richardson, P. G., H. Briemberg, S. Jagannath, P. Y. Wen, B. Barlogie, J. Berenson, S. Singhal, D. S. Siegel, D. Irwin, M. Schuster, G. Srkalovic, R. Alexanian, S. V. Rajkumar, S. Limentani, M. Alsina, R. Z. Orlowski, K. Najarian, D. Esseltine, K. C. Anderson and A. A. Amato (2006). "Frequency, characteristics, and reversibility of peripheral neuropathy during treatment of advanced multiple myeloma with bortezomib." J Clin Oncol **24**(19): 3113-3120.
Schafer, P. H., A. K. Gandhi, M. A. Loveland, R. S. Chen, H. W. Man, P. P. Schnetkamp, G. Wolbring, S. Govinda, L. G. Corral, F. Payvandi, G. W. Muller and D. I. Stirling (2003). "Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs." J Pharmacol Exp Ther **305**(3): 1222-1232.
Weber, D. M., C. Chen, R. Niesvizky, M. Wang, A. Belch, E. A. Stadtmauer, D. Siegel, I. Borrello, S. V. Rajkumar, A. A. Chanan-Khan, S. Lonial, Z. Yu, J. Patin, M. Olesnyckyj, J. B. Zeldis, R. D. Knight and I. Multiple Myeloma Study (2007). "Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America." N Engl J Med **357**(21): 2133-2142.
Weisel, K. C., J. San Miguel, G. Cook, M. Leiba, K. Suzuki, S. Kumar, M. Cavo, H. Avet-Loiseau, H. Quach, V. Hungria, S. Lentzsch, R. Hajek, P. Sonneveld, K. Wu, Q. Qin, C. Chiu, D. Soong, M. Qi, J. M. Schecter and M. A. and Dimopoulos (2017). Efficacy of daratumumab in combination with lenalidomide plus dexamethasone (DRd) or bortezomib plus dexamethasone (DVd) in relapsed or refractory multiple myeloma (RRMM) based on cytogenetic risk status, Journal of Clinical Oncology. **35:** 8006-8006
Mateos, M.V. Nahi, H. Legiec, W. Grosicki, S. Vorobyev, V. Spicka, I. Hungria, Vania. Korenkova, S. Bahlis, N. Flogegard, M. Bladé, J. Moreau, P. Kaiser, M. Iida, S. Laubach, J. Magen, H. Cavo, M. Hulin, C. Usmani, S. "Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multi-centre, open-label, non-inferiority, randomised phase 3 trial." The Lancet Haemotology Volume 7 Issue 5, May 2020 370-380.

20.0 APPENDICES

Appendix A ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix B Durie Salmon Stage and International Staging System (ISS) for Multiple Myeloma

Stage	Durie Salmon Stage	ISS Stage
I	All of the following: Hemoglobin value >10 g/dL Serum calcium value normal or ≤12 mg/dL Bone x-ray, 0-1 lesion or solitary bone plasmacytoma only Low M-component production rate — IgG value <5 g/dL; IgA value <3 g/Dl; urine light chain M-component on electrophoresis <4 g/24 h	Serum β_2-microglobulin < 3.5 mg/L AND Serum albumin > 3.5 g/dL
II	Neither stage I nor stage III	Serum β_2-microglobulin <3.5 mg/L, but serum albumin <3.5 g/dL OR Serum β_2-microglobulin 3.5 to <5.5 mg/L, irrespective of serum albumin
III	One or more of the following: Hemoglobin value <8.5 g/dL Serum calcium value >12 mg/dL Advanced lytic bone lesions (> 3 lesions) High M-component production rate — IgG value >7 g/dL; IgA value >5 g/dL — Bence Jones protein >12 g/24 h	Serum β_2-microglobulin >5.5 mg/L

Adapted from (Durie and Salmon 1975, Greipp, San Miguel et al. 2005)

Appendix C FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

Appendix D EQ-5D-3L Questionnaire

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

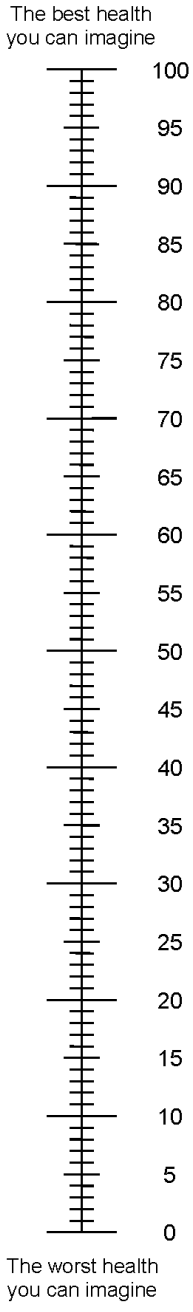
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide.

Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

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

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). The investigator must ensure that:

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

Contraception

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

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

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

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

contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

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

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

Before starting lenalidomide

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

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

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:
- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:
- Male condom
- Diaphragm
- Cervical Cap

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

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

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

Before starting lenalidomide

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

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

During study participation and for 28 days following lenalidomide discontinuation

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

Male Patients:
- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.
- Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.

<u>Additional precautions</u>
- Patients should be instructed never to give lenalidomide to another person.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- Any unused lenalidomide must be returned as instructed through Revlimid REMS® program.

Appendix F: Contingency Operations Plan

1.0 Introduction

In the event of a public health or civil emergency or restrictions clinical changes may be necessary to effectively manage the study. Should such an instance occur, participating sites will be informed that the following adjustments may be applied as required to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure).

2.0 Study/Subject Management

It is important that specific information explaining the basis for missing data be recorded in the eCRF (citing the relationship to the event/restrictions, as applicable). Directives for the process to be followed will be communicated by the UM Coordinating Center.

A. Disease Testing:

Infectious disease (i.e. COVID-19 testing) is not currently being added to the protocol as part of the screening requirements, but may be done as part of the clinical assessment, as needed during the course of the pandemic. Infectious disease tests/results will be recorded in the subject's source documents but will only be added as an Adverse/ Serious Adverse Event in the eCRF should the test yield a positive result.

B. New Subject Enrollment:

Together with the study Supporter, the Sponsor-Investigator will evaluate the new benefit/risk for subjects on the trial and determine if study enrollment needs to be partially or completely paused.

While the study may permit new subject enrollments, participating sites and/or respective IRBs of record may determine new enrollments are not allowed. If that is the case, written documentation of such a determination is to be shared with the UM Coordinating Center and the respective IRB of record per local guidance.

C. Study Visit Schedules/Schedule of Events

During a public health or civil emergency, and in accordance with regulatory requirements, temporary visit adjustments may be made at the site level specific to the scenario (e.g., virtual visits per clinician/subject discretion). For instances where protocol-specified assessments cannot be made and/or data are unable to be collected, the study team is expected to document the specific reason(s) (e.g., identifying the specific limitation imposed by the restrictions leading to the inability to perform the protocol-specified assessment), and report as appropriate. For reporting to Coordinating Center, this should be documented using the Protocol Deviation form.

D. Laboratory Assessments

It may be possible that lab closure is required as a contingency measure during the course of a public health or civil emergency or restrictions. Should that occur:

- All institutional requirements regarding in person contact with subjects and facility closures (including laboratories) will be followed. Research blood samples will not be collected or

processed when labs are closed or under restrictions due to public health or civil emergency restrictions.

- Standard of care laboratory assessments may be drawn at a local laboratory per clinician/subject discretion.

E. Informed Consent Form (ICF)

Sites should communicate all changes to the research plan to the subject, as applicable, and must do so if the changes might affect the subject's willingness to continue participation in the study. Documentation of the discussion and the subject's decision to continue/discontinue should be documented in the subject's record.

F. Statistical Analytics Plan

Should changes in the contingency operation plan and/or protocol lead to amending the statistical analysis plan for this study, consideration for doing so will include submission and/or consultation with the applicable committees and regulatory agencies for review.

The plan for protocol deviations related to public health or civil emergency or restrictions will be assessed as part of the pre-specified analyses and statistical procedures for handling these deviations will be addressed in the statistical analysis plan prior to database lock. Revisions to the statistical plan will be updated in the protocol and the statistical analysis plan, as required.

3.0 Monitoring

The O-CTSU Multi-Site Project Management Team (Coordinating Center) will oversee the progress of this clinical trial and ensure that it is conducted, recorded and reported in accordance with the applicable regulatory requirements.

This Contingency Operations Plan will be performed in conjunction with the Clinical Monitoring Plan as well as internal University of Michigan Rogel Cancer Center O-CTSU policies and procedures, and will be performed by qualified O-CTSU Multi-Site Project Managers (MSPMs) or their designee.

Planned on-site monitoring visits may not be possible if the restrictions put in place limit travel and/or access to site location. As such, remote monitoring will be performed as necessary to maintain the defined monitoring cadence, noting electronic medical record (EMR) access and/or sending of redacted source documents will be necessary. Should such records not be made available, to maintain oversight of clinical sites centralized review of data entry, safety/adverse event data, and protocol deviations (at a minimum) will be assessed and reported to the Sponsor-Investigator and study site.

Eligibility checklist and supporting redacted source document review will remain in place to confirm IC process and subject eligibility prior to study enrollment.

4.0 Safety and Protocol Deviation Reporting

All safety and protocol deviation reporting for the study remains in place, per protocol requirements. Participating sites are to follow the current requirements as well as any additional requirements per their IRB of record and provide documentation and/or url links to their respective IRB of Record to the UM Coordinating Center. Documentation of required reporting timelines are to be utilized during monitoring.

Appendix G: COVID-19 Survey

Subject ID:	
Date(mm/dd/yyyy):	

COVID19 VACCINE, INFECTION, TREATMENT SURVEY *:Date(s)	Vaccine (1st, 2nd, booster 1, 2)	Vaccine type	Evusheld (1st, 2nd)	Positive covid test type (Ag vs PCR)	Infection symptom duration	Covid19 treatment	Covid19 treatment agents	Post-treatment covid test (if done)

*if data not available: please enter “not done”, or “record not available”. Approximate dates are acceptable as some data are retrospectively collected given the timing and dynamic changes during pandemic.