MSK PROTOCOL COVER SHEET

Short Course Daratumumab in Minimal Residual Disease (MRD) Positive Myeloma Patients After Induction Therapy With/Without Consolidative High Dose Chemotherapy/Autologous Stem Cell Support

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Table of Contents

1.1 PROTOCOL SUMMARY AND/OR SCHEMA

Primary Objective This is a phase II study to assess the efficacy of short course daratumumab in multiple myeloma patients with minimal residual disease (MRD) positivity after induction therapy with/without consolidative autologous stem cell transplant (ASCT). Primary objective of the study will be to determine the rate of MRD negativity by the completion of 6 months of daratumumab therapy.

Secondary Objectives:

1. To assess the rate of sustained MRD negativity in the bone marrow.
2. To determine duration of MRD negativity
3. To compare MRD techniques of multi-parametric flow cytometry with next-generation sequencing and mass spectrometry.
4. To determine progression-free and overall survival

Exploratory Studies:

1. The gene panel MyType (or comparable next generation sequencing panel) will explore whether any mutations appear to be associated with response to therapy or toxicity associated with therapy.

2. MyType(or comparable next generation sequencing panel) will also be evaluated using samples at the time of progression of disease and will be compared to the pre-treatment baseline samples to explore whether pathways leading to emergence of resistance to the drug regimen can be identified.

Patient Population

The proposed study will enroll newly diagnosed multiple myeloma patients achieving a very good partial response (VGPR) or better with MRD positivity by flow cytometry after induction therapy with/without ASCT as well patients previously MRD negative for at least 3 months (after induction and consolidation therapy) and have turned MRD positive by flow cytometry with no evidence of progressive disease. All patients must be on standard of care lenalidomide maintenance for at least 6 months at the time of enrollment.

Study Design

- Single arm phase II trial of daratumumab for MRD positive multiple myeloma patients currently receiving standard of care lenalidomide maintenance therapy.
- Daratumumab is administered weekly for cycles 1 and 2 and bi-weekly for the remaining 4 cycles..
- Bone marrow biopsy will be obtained at baseline for confirmation of diagnosis and correlative studies. A follow-up bone marrow biopsy will be performed at the completion of treatment or at disease progression.

- Patients will also undergo evaluation for response at monthly intervals using traditional IMW uniform response criteria (Kumar. et al. Lancet Oncology 2016) with serum and urine protein electrophoresis, immunofixation, and serum free light chains (FLC).
- Patients will continue standard of care lenalidomide maintenance during the protocol and after completing daratumumab as recommended by the treating physician.

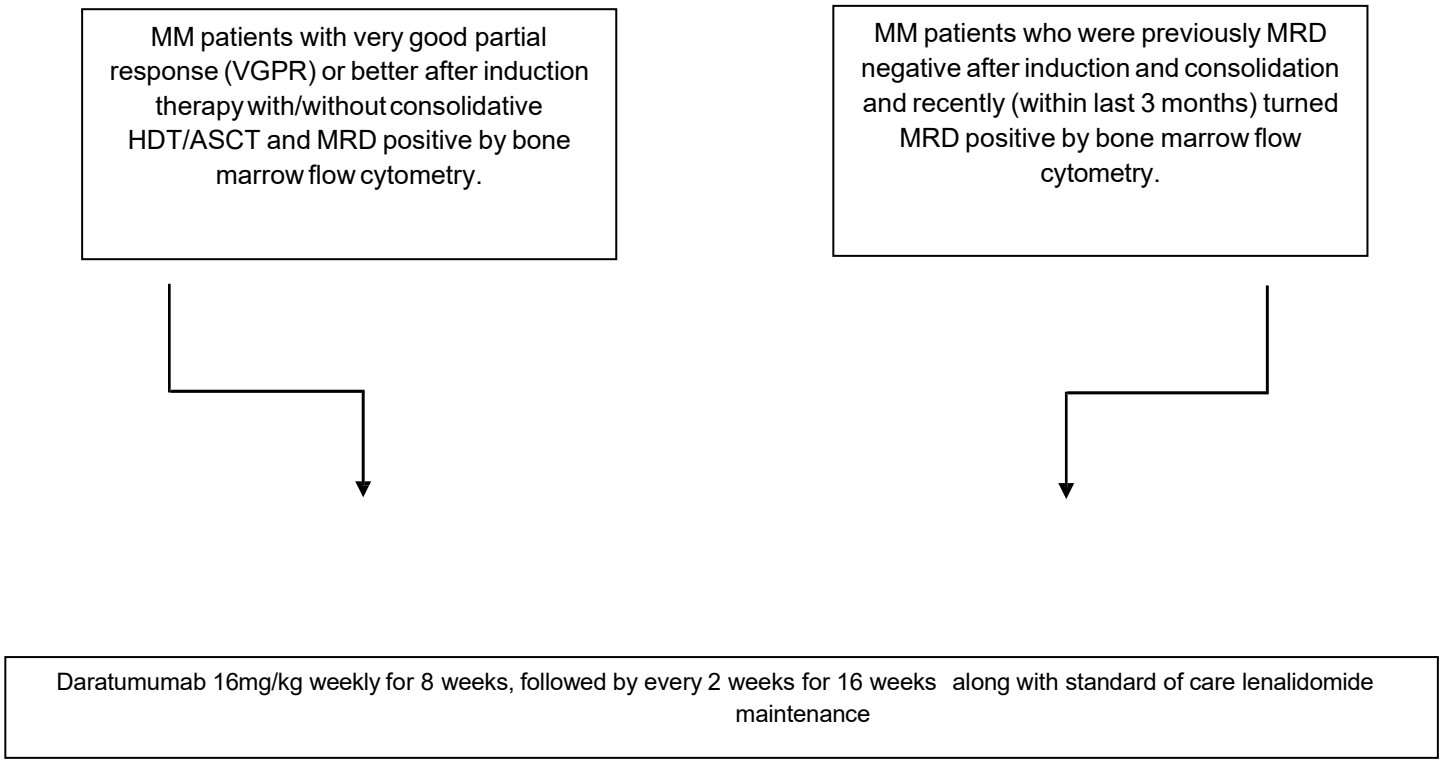
Statistics

The primary objective of this trial is to determine whether treatment with daratumumab is associated with a substantial fraction of patients with MRD positive multiple myeloma converting to a MRD negative state as assessed by multicolor flow cytometry. Previously studies have reported that approximately 10% of patients will achieve deeper responses including MRD negativity after maintenance therapy with lenalidomide alone[29]. The current study will be considered positive if the rate of MRD negativity is 30% or higher with daratumumab. This study will implement a Simon's two-stage minimax design to distinguish between an unpromising rate of 10% and a promising rate of 30%. The study is designed to have a type I error and a type II error of 0.10. The maximum sample size is 25 patients

Treatment Plan (see schema below)

- Cycles 1 and 2: Daratumumab 16mg/kg weekly as intravenous infusion (total duration: 8 weeks)
- Cycles 3-6: Daratumumab 16mg/kg once every 2 weeks as intravenous infusion (total duration: 16 weeks)
- Lenalidomide maintenance therapy to be administered as standard treatment to all patients. This is administered as 5-15 mg daily 21-28/28 day cycle.

Schema


MM patients with very good partial response (VGPR) or better after induction therapy with/without consolidative HDT/ASCT and MRD positive by bone marrow flow cytometry.
MM patients who were previously MRD negative after induction and consolidation and recently (within last 3 months) turned MRD positive by bone marrow flow cytometry.
Daratumumab 16mg/kg weekly for 8 weeks, followed by every 2 weeks for 16 weeks along with standard of care lenalidomide maintenance

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

This is a phase II study to assess the efficacy of short course daratumumab in multiple myeloma patients with minimal residual disease (MRD) positivity after induction therapy with/without consolidative autologous stem cell transplant (ASCT). Primary objective of the study will be to determine the rate of MRD negativity by the completion of 6 months of daratumumab therapy.

Secondary Objectives:

1. To assess the rate of sustained MRD negativity in the bone marrow).
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1. The gene panel MyType(or comparable next generation sequencing panel) will explore whether any mutations appear to be associated with response to therapy or toxicity associated with therapy.

2. MyType will (or comparable next generation sequencing panel) also be evaluated using samples at the time of progression of disease and will be compared to the pre-treatment baseline samples to explore whether pathways leading to emergence of resistance to the drug regimen can be identified.

3.0 BACKGROUND AND RATIONALE

3.1 Introduction

Multiple Myeloma and daratumumab

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

CD38 is a 45-kD, type II transmembrane glycoprotein that associates with cell-surface receptors in lipid rafts, regulates cytoplasmic Ca^{2+} flux, and mediates signal transduction in lymphoid and myeloid cells[5,6]. CD38 is highly and uniformly expressed on myeloma cells[7,8] and is expressed at relatively low levels on normal lymphoid and myeloid cells and in some tissues of nonhematopoietic origin, which makes it a potential target in the treatment of myeloma[6]. Daratumumab (HuMax-CD38, Genmab), a human IgG1κ monoclonal antibody, binds to a unique CD38 epitope[9]. Preclinical studies showed that daratumumab induced target-cell killing of CD38-expressing tumor cells by means of multiple mechanisms, including complement-mediated and antibody-dependent cell-mediated cytotoxic effects, antibody-dependent cellular phagocytosis, apoptosis[9,10], and to a lesser extent, inhibition of the enzymatic activity of CD38.

Early phase clinical trials have established the single agent activity and efficacy of this drug in patients with relapsed and/or refractory myeloma patients[11]. Furthermore, the drug is fairly well tolerated with infusion related reactions being the most common adverse events[11]. Daratumumab was approved by the FDA as monotherapy for patients with relapsed/refractory multiple myeloma in November 2015. This approval was based on a single arm phase trial with 106 patients that demonstrated an objective response rate of 29% with median duration of response of 7.4 months.

Daratumumab in Combination with Lenalidomide and Dexamethasone

More recently, Dimopoulos et al published the results of a Phase 3 study in patients with multiple myeloma with one or more prior lines of therapy randomized to receive lenalidomide (Revlimid®) and dexamethasone either alone or in combination with daratumumab[12]. The estimated 12 month progression-free survival was 83.2% of patients receiving the three drug combination compared to 60.1% amongst patients receiving lenalidomide and dexamethasone only[12]. Daratumumab was approved by the FDA in combination with lenalidomide and dexamethasone for patients with relapsed/refractory multiple myeloma in November 2016. However, daratumumab is not currently approved by the FDA for the indication under the current study i.e. patients with MRD positivity after induction therapy with/without consolidative HDT/ASCT.

Minimal Residual Disease Testing in Myeloma

In the past decade, multiple myeloma patients have reached deeper response rates with use of effective anti-myeloma therapeutics, immunomodulatory agents and proteasome inhibitors, approximating up to 75% patients achieving near-complete response (>90% decrease in monoclonal protein) or complete response (100% decrease in monoclonal protein). In general, improved therapeutics and deeper response rates have resulted in improved overall survival of multiple myeloma patients across most age groups. As a result, there has been an increasing interest for the development of sensitive assays to detect minimal residual disease (MRD) in treated MM patients[13]. In MM patients, MRD-negative status using multi-parametric flow cytometry (MFC) is associated with improved progression free survival and overall survival[14,15]. Similar studies using next generation sequencing methods for MRD have also been shown to be associated with improved outcomes in MM MRD-negative patients.

Minimal Residual Disease Platforms

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

In 2015, the Department of Laboratory Medicine developed, validated and implemented the 10-color flow cytometry platform in collaboration with the Myeloma Service and the International Myeloma Foundation. The MSK single tube 10-color flow cytometry platform demonstrates similar results to Euroflow and is already in use under clinical practice[17] . Because there is currently no data available to compare the sensitivity of the MSK model and molecular MRD assays, as a secondary endpoint, we will compare our 10-color flow cytometry platform against next generation sequencing and mass spectrometry. These studies will help us to better understand and further develop details of various MRD methods.

3.2 Proposed Study Investigation with Correlative Studies

MRD negativity after induction (with/without consolidative ASCT) is an increasingly important outcome for patients with multiple myeloma. The management of low burden disease (VGPR or better) after initial induction and during maintenance therapy is unclear at this time. In the current study, we propose short course daratumumab for newly diagnosed MM patients with very good partial response (VGPR) or better after induction therapy with/without consolidative HDT/ASCT and MRD positive by bone marrow flow cytometry and for patients who were previously MRD negative after induction and consolidation and recently (within last 3 months) turned MRD positive (with no evidence of clinical progression) by bone marrow flow cytometry. All patients must be on standard of care lenalidomide maintenance for at least 6 months at the time of enrollment

All patients will receive a total of 24 weeks of daratumumab therapy (16 mg/kg intravenous infusion weekly for 8 weeks followed by every 2 weeks for 16 weeks) and continue standard of care lenalidomide maintenance therapy. Baseline studies will include bone marrow biopsy and aspirates with the first pulled bone marrow sample sent for multi-parametric flow cytometry as a priority sample to determine MRD status and determine eligibility. Upon completion of protocol therapy or when patients achieve sCR, patients will undergo a repeat bone marrow biopsy and aspirate for MRD assessment and correlative studies.

The study is powered to assess efficacy (as determined by rate of MRD negativity) of daratumumab in combination with standard of care lenalidomide maintenance amongst patients with low burden disease (i.e. MRD positivity). Our study is novel since no prior myeloma study has been designed to target MRD positive disease with the primary endpoint of achieving status MRD negativity. Secondary endpoints include evaluation of sustain MRD negativity, progression-free survival, overall-survival, and comparison of MRD platforms. Based on the rapidly evolving field with new powerful drugs, the anticipation is that MRD will become a new endpoint for future myeloma trials. MSK myeloma service is a global leader in this context.

3.3 Federal Regulations: The Privacy Rule

In the case of research repositories of tissue and biological specimens, the collection of such samples is treated as research under the Privacy Standards (67 Fed Reg 53231; HIPAA Privacy Rule and Public Health: Guidance from CGC and HHS). Under HIPAA, all subjects must agree to sign research authorizations that describe the uses and disclosures of their protected health information, as well as informed consents that describe the risks and benefits of participating in the study. It is not acceptable to sign one or the other. Both documents must be signed by the subject to be considered a valid study participant (45 CFR 164.508(b)(3)).

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

3.4 Office of Human Research Protections Guidance

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

3.5 New York State Law

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

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

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

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single arm phase II study to investigate the efficacy of short course daratumuab for patients who are MRD positive. Patients with MM with very good partial response (VGPR) or better after induction therapy with/without consolidative HDT/ASCT and MRD positive by bone marrow flow cytometry and MM patients who were previously MRD negative after induction and consolidation and recently (within last 3 months) turned MRD positive by bone marrow flow cytometry will be enrolled.

4.3 Intervention

- Cycles 1 and 2: Daratumumab 16mg/kg weekly per cycle (28 days) as intravenous infusion (total duration: 8 weeks)
- Cycles 3-6: Daratumumab 16mg/kg once every 2 weeks per cycle (28 days) as intravenous infusion (total duration: 16 weeks)
- Lenalidomide maintenance therapy to be administered as standard treatment to all patients. This is administered as 5-15 mg daily 21-28/28day cycle.
- Premedications:
  - Dexamethasone 20mg/dose IV on Days 1, 8, 15, 22 for Cycles 1 and 2 and Day 1 and Day 15 for Cycles 3-6.
  - Montelukast 10mg PO for the first 4 weeks
  - Tylenol 650 mg PO prior to each dose of daratumumab
  - Benadryl 25 mg PO prior to each dose of daratumumab

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 Daratumumab

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

Daratumumab induces lysis of CD38-expressing tumor cells, by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), through activation of complement proteins, natural killer (NK) cells, and macrophages, respectively[9,10]. For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding daratumumab, refer to the latest version of the Investigator's Brochure [Daratumumab IB].

Preliminary pharmacodynamic studies suggest that daratumumab utilizes multiple effector cell functions, resulting in immune mediated killing of CD38-expressing tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary CD38-expressing MM cells, complement-dependent cytotoxicity(CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody- mediated activation of the complement proteins[9] . Daratumumab-induced antibody- dependent cell-mediated cytotoxicity (ADCC) is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro (de Weers 2011)[2] . Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro (Overdijk 2013)[10]. Further, in vitro studies indicated that daratumumab inhibited the cyclase activity of CD38 and stimulated the CD38 hydrolase activity (Study No. GMB 3003-013). Daratumumab induces the elimination of CD38+ populations of Tregs, Bregs and MDSCs and is hypothesized to support the clonal expansion of effector T cells.

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

In general, daratumumab is tolerated well. Maximum tolerated dose (MTD) has not been reached following intravenous (IV) infusions up to 24 mg/kg monotherapy and 16 mg/kg in combination studies. The most frequently reported adverse events (AEs) across the daratumumab program have been infusion-related reactions (IRRs) following single agent therapy. Among all subjects treated in ongoing studies (monotherapy and combination therapy), IRRs have been reported in 49% of subjects; among 151 subjects treated with 16 mg/kg daratumumab monotherapy in Studies GEN501 and MMY2002, the percentage

of subjects with a reported IRR was identical (49%) to what was observed across all treated subjects. The most frequently reported AEs (reported in ≥5% of subjects) reported as IRRs were rhinitis allergic (8%), cough (7%), and nasal congestion (6%). Among subjects treated with 16 mg/kg daratumumab monotherapy, the most commonly reported IRRs were nasal congestion (8%), cough (7%), and rhinitis allergic and throat irritation (5% each). Grade 3 or higher IRRs were reported in 5% of subjects treated with 16 mg/kg daratumumab as monotherapy, with bronchospasm and hypertension being the most frequently reported Grade 3 or higher IRRs (1% each).

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

Among the 151 subjects treated with 16 mg/kg daratumumab as monotherapy in Studies GEN501 and MMY2002, the most frequently reported AEs (reported in >10% of subjects) were fatigue (29%); anemia (23%); nausea (19%); back pain (18%); cough (17%); thrombocytopenia (16%); decreased appetite (13%); pyrexia, dyspnea, upper respiratory tract infection (12% each); nasal congestion and neutropenia (11% each). Grade 3 and higher AEs were reported in 48% of subjects treated with 16 mg/kg monotherapy daratumumab. The most frequently reported Grade 3 or higher AEs were anemia (13%) and thrombocytopenia (9%). All other Grade 3 and higher AEs were reported in <5% of subjects. No deaths due to daratumumab-related AEs have been reported in any ongoing study.

Among the 283 patients who received daratumumab in combination with lenalidomide and dexamethasone in the POLLUX trial[12], please see Table 7 and Table 8 (DRd (N=283) %) for the most frequently reported AEs (reported in >10% of subjects) and the most frequently reported Grade 3 or higher AEs. All other Grade 3 and higher AEs were reported in <5% of subjects.

Table 7: Adverse reactions reported in ≥ 10% of patients and with at least a 5% greater frequency in the DRd arm in POLLUX

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

Table 8: Treatment-emergent hematology laboratory abnormalities in POLLUX

	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any 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.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

6.2 Subject Inclusion Criteria

1. Patients with a diagnosis of Multiple Myeloma who have achieved a VGPR or better (based on best response) after induction with or without consolidation therapy/ HDT ASCT

2. MRD positive at screening by flow cytometry

3. Additionally, patients who were previously MRD negative after induction therapy with/without consolidative HDT/ASCT and have turned MRD positive (by flow cytometry) based on bone marrow done at screening and do not have any evidence of progressive disease are eligible.

4. Patients must be on standard of care lenalidomide maintenance therapy for at least 6 months at the time of study enrollment.

5. Patient can be receiving bisphosphonate therapy per the treating oncologist's discretion.

6. Creatinine clearance ≥45 ml/min using the Cockcroft-Gault method, MDRD, or CKD-EPI formula. If the calculated CrCl based on Cockcroft-Gault method, MDRD, or CKD-EPI is <45 mL/min, patient will have a 24 hr urine collection to measure CrCl.

7. Age ≥18 years.

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

9. Male or female patient who accepts and is able to use recognized effective contraception (oral contraceptives, IUCD, barrier method of contraception in conjunction with spermicidal jelly) throughout the study when relevant.

10. Absolute neutrophil count (ANC) ≥1.0 x 10^9 /L, hemoglobin ≥8 g/dL, and platelet count ≥75 x 10^9/L. No transfusion or growth factor support for one week prior to labs.

11. Adequate hepatic function, with bilirubin < 1.5 x the ULN, and AST and ALT < 2.5 x ULN

6.3 Subject Exclusion Criteria

Patients will not be eligible for the study if they fulfil one or more of the following exclusion criteria:

1. Patients with a diagnosis of MM not achieving a VGPR or better to the most recent therapy.

2. Patients with a diagnosis of MM who are MRD Negative by flow cytometry

3. Patients must not have measurable disease at the time of enrollment. Measurable disease is defined as follows-
    - Serum monoclonal protein > 0.5gm/dL
    - Urine monoclonal protein >200 mg/24 hours
    - Involved serum free light chain > 10 mg/dL

4. Pregnant or lactating females.

5. Uncontrolled hypertension or diabetes.

6. Has significant cardiovascular disease with NYHA Class III or IV symptoms, or hypertrophic cardiomegaly, or restrictive cardiomegaly, or myocardial infarction within 3 months prior to enrollment, or unstable angina, or unstable arrhythmia.

7. Uncontrolled intercurrent illness including but not limited to active infection or psychiatric illness/social situations that would compromise compliance of study requirements.

8. Active infection requiring treatment within two weeks prior to first dose.

9. Contraindication to any concomitant medication, including antivirals, anticoagulation prophylaxis, tumor lysis prophylaxis, or hydration given prior to therapy.

10. Major surgery within 1 month prior to enrolment.

11. Previous therapy with daratumumab or other anti-CD38 monoclonal antibodies.

12. History of other malignancy (apart from basal cell carcinoma of the skin, or in situ cervix carcinoma) except if the patient has been free of symptoms and without active therapy during at least 5 years.

13. Active hepatitis B or C infection.

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

7.0 RECRUITMENT PLAN

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

8.1 PRETREATMENT EVALUATION

- A complete history and physical examination with documentation of measurable disease and assessment of performance status using the ECOG scale must be performed within 4 weeks prior to study entry

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

- CBC with differential and reticulocyte count
- Chem 14, Magnesium, and Phosphate and eGFR determination
- Uric acid, LDH, and Beta-2 Microglobulin
- PT, PTT
- Serum protein electrophoresis (SPEP) and immunofixation to assess for presence and quantity of monoclonal protein (M-protein)
- 24 hour urine sample for protein electrophoresis (UPEP) and immunofixation to assess for monoclonal protein in the urine (Bence-Jones proteinuria) at baseline.
- Serum free light-chain studies, determined using the FreeliteTM assay system

- Quantitative immunoglobulins
- Review of bone marrow core biopsy and aspirate.
- Serum or urine pregnancy test in women of child-bearing potential.
- 12-lead EKG
- *Optional* Echocardiogram – 2D Echo or strain echo (Please refer to Section 10.0)
- Viral serologies
  - Hepatitis B surface antigen (HBsAg)
  - Hepatitis B surface antibody (Anti-HBs)
  - Hepatitis B core antibody (Anti-HBc)
  - Anti-Hepatitis C (HCV) antibody. If positive, will follow with HCV RNA PCR

HBV Serology

- All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening as indicated above.
- Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment when Protocol Amendment 03 is implemented will be required to have HBV serology performed locally upon signing the updated ICF.
  - HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose.

HBV DNA Tests:

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

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

- Bone Marrow
  - Histopathological evaluation on bone marrow aspirate and biopsy
  - Immunophenotyping of aberrant clonal plasma cells by multiparametric flow cytometry.
  - Immunoglobulin heavy and/or light chain rearrangement.
  - Interphase FISH/cytogenetics
  - Index clone identification for NGS MRD evaluation.

- Peripheral Blood/Urine
  - Peripheral blood and urine samples for storage and establishing a biobank.

- Immune cells – including, but not limited to T cells (CD4 and CD8), LGL, and NK cells.

Imaging (FDG/PET/CT scan) within 4 weeks of study entry and prior to starting therapy
Prior to ^{18}F-FDG PET/CT imaging, the subject will be fasted and have not received any sugar containing substance (i.e. glucose, sucrose, dextrose) for 4-6 hours. Subjects will be encouraged to drink water during this period to reduce radiation dose to the kidneys and will be asked to void prior to ^{18}F-FDG injection. Women of childbearing potential will have a documented report of negative pregnancy test before the scan.

^{18}F-FDG, [18F]-fludeoxyglucose is an FDA approved radiopharmaceutical. Immediately prior to injection, the subject's blood glucose level will be evaluated via fingerstick. Non-diabetic subjects with fasting blood glucose levels above 200 mg/dl may be rescheduled at the discretion of the PI. Subjects will be asked to refrain from excessive physical exertion for the 24 hours prior to injection.

PET-CT performed within the 4 weeks at an outside institution can be acceptable as baseline study as long as the images are uploaded in PACS and reviewed at MSKCC.

9.1 TREATMENT/INTERVENTION PLAN

Patients who have signed the consent form and are deemed eligible for this clinical trial will start therapy with daratumumab with the following schedule:

- Cycles 1 and 2: Daratumumab 16mg/kg weekly for 4 weeks as intravenous infusion
- Cycles 3-6: Daratumumab 16mg/kg once every 2 weeks for 4 weeks as intravenous infusion
- Lenalidomide maintenance therapy to be administered as standard treatment to all patients.
- Premedications:
  - Dexamethasone 20mg/dose IV on Days 1, 8, 15, 22 for Cycles 1 and 2 and Day 1 and 15 for Cycles 3-6. Montelukast 10mg PO for the first 4 weeks
  - Tylenol 650 mg PO prior to each dose of daratumumab
  - Benadryl 25 mg PO prior to each dose of daratumumab

Recommended Concomitant Medications:

- Post-infusion Medications:
  - Administer post-infusion medication to reduce the risk of delayed infusion reactions to all patients as follows:
    - Oral dexamethasone 4 mg (e.g. methylprednisolone 20 mg or equivalent) daily for two days starting the day after infusion.

- Prophylaxis for Herpes Zoster Reactivation
  - Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting DARZALEX 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 see Section 10.0
  - For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

Infusion Related Reaction (IRR) Management - Daratumumab

Severe infusion reactions associated with Daratumumab include bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension. Patients will be pre-medicated with antihistamines, antipyretics and corticosteroids and frequently monitored during entire infusion. Infusions will be interrupted for interactions of any severity and medical management will be managed. Daratumumab will be permanently discontinued for life-threatening (Grade 4) reactions. For patients with Grade 1, 2, or 3 reactions, the infusion rate will be reduced when re-starting the infusion. To reduce the risk of delayed infusion reactions, corticosteroids will be given to all patients.)]. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. In these instances post-infusion short and long-acting bronchodilators, and inhaled corticosteroids medications maybe prescribed. If the patient experiences no major infusion reactions, following the first four infusions, these additional inhaled post-infusion medications may be discontinued.

9.1. Hematologic Toxicity

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

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

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

- The next cycle of treatment will not be initiated until the above conditions (section 9.3.1) are met. If ANC and platelet counts do not satisfy the requirements above after 2 weeks of withholding treatment, the subject will go off therapy. Transfusions and growth factors are permissible.

9.2 Non-Hematologic Toxicities Requiring Dosing Modifications

9.2.1 Any ≥Grade 3 non-hematologic toxicity require daratumumab to be held until resolved to Grade 1 or baseline prior to resuming therapy or initiating next cycle. Investigator will determine which drug will be held based on side effect profile and clinical judgment. If therapy has been held for more than 3 weeks due to non-hematologic toxicity, the patient will be removed from protocol therapy.

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

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

9.3 Monitoring

9.3.1 Routine labs (CBC, chemistry panel 14, LDH, magnesium, uric acid, phosphate) will be performed every 2 weeks for the first 2 cycles, then on day 1 for cycle 3-6, at end of therapy. Myeloma tests include serum protein electrophoresis, serum immunofixation, beta-2 microglobulin, quantitative immunoglobulins and serum free light chains assay will be performed at baseline, start of each cycle, at end of therapy. Routine labs, and myeloma labs can be performed 24 hrs in advance.

9.3.2 Patients will have clinic visits with H&P or standard progress notes assessing for toxicity/side effects at baseline, day 1 of each cycle, end of therapy, 1-month after end of therapy. Treatment window for day 1 of start of each cycle is +/- 7 days. Treatment window for intra-cycle daratumumab doses is +/- 2 days.

9.3.3 24-hr urine sample for protein electrophoresis (UPEP) and immunofixation will be performed at baseline

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

9.3.5 An Echocardiogram (2-D or strain echo) is optional at baseline (Please refer to Section 10.0).
Outside echocardiograms are permissible

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

9.3.7 PFS and OS data will be collected for patients.

9.4 After Protocol Therapy

9.4.1 Upon completion of protocol therapy, patients will be encouraged to continue lenalidomide maintenance as standard of care treatment.

CONCOMITANT MEDICATIONS/MEASURES

BONE DISEASE

1) Bisphosphonate therapy: Approved bisphosphonate therapy (zoledronic acid or pamidronate) is allowed. Patients will be monitored for renal function and osteonecrosis of the jaw. Patients may require prior evaluation from dental specialist before instituting bisphosphonates.

TRANSFUSIONS/GROWTH FACTORS

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

ANTI-COAGULATION

Oral Aspirin 81 mg or 325 mg or suitable alternative anti-coagulation for thrombotic prophylaxis as standard of care for lenalidomide.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Study	Pre-Treatment	Induction Treatment							End of therapy [j,k]		Follow-up	
		Cycle 1-2				Cycles 3-6				1 month after end of therapy [i,h,k]		
		Day 1 [k]	Day 8	Day 15	Day 22	Day 1 [k]	Day 15	CR/sCR reached				
Medical Record Review	x								x	x		
H&P with blood pressure	x	x				x			x	x		
EKG	x											
Echo	x [m]											
ECOG	x					x			x			
Informed Consent	x											
Viral Studies [b]	x [b]					x [b]			x [b]	x [b]		
Routine Labs [a]	x [n]	x [n]		x		x			x			
Lymphocyte subsets	x								x			
Myeloma tests [e,i]	x [e,l,n]	x [n]				x [e,i]			x [e,l]			
Urine for UPEP and IFE [i]	x [i,n]	x [n]				x [i]			x [i]			
Pregnancy Test [c]	x [c]	x				x [c]						
Research Blood/Urine [d]		x	x	x	x	x		x	x			
Bone Marrow/Aspirate	x							x [p]	x [g,p]			
FDG PET-CT [j]	x								x [j]			
Adverse Events/Toxicity		x				x			x	x		

a. Routine tests include CBC, reticulocyte count, Chem 14, magnesium, phosphate, uric acid, eGFR determination and LDH. Reticulocyte count will only be performed at baseline, day 1 of every cycle, and end of therapy. PT and PTT will only be performed at baseline. Peripheral blood lymphocyte subsets at baseline, C4D1, and end of therapy
b. Viral studies include Hep B surface antigen, Hep B surface antibody, Hep B core antibody and Hep C antibody. If Hep C antibody positive, Hep C RNA PCR will be performed. Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Treatment phase: Q12W during treatment, at End of Treatment, and Q12W for up to 6 months after the last dose of study treatment.
c. Pregnancy tests (urine or serum) for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months)
d. To be stored at MSKCC HOTB biobank.
e. Myeloma tests include serum protein electrophoresis, serum immunofixation, 24-hr urine electrophoresis, urine immunofixation, serum free light chains, quantitative immunoglobulins, beta-2 microglobulin and will be performed at baseline.
f. Bone marrow aspiration and biopsy will be sent for histopathology, flow cytometry, FISH/cytogenetics. Lysate will also be sent for cell sorting into CD 138- and + fractions and whole bone marrow lysate for HOTB storage so molecular profiling with GEP and DNA-based sequencing at baseline can be performed as correlative work.
g. Bone marrow aspirate and biopsy can be performed +/- 21 days of intended cycle day or achievement of CR/sCR. Bone marrow aspirate and biopsy will be sent to evaluate for histopathology, flow cytometry (bone marrow immunophenotyping of plasma cells), heavy/light chain immunoglobulin rearrangement. Aspirate lysate will also be sent for cell sorting into CD 138- and + fractions and whole bone marrow lysate for HOTB storage so molecular profiling with GEP and DNA-based sequencing at baseline can be performed as correlative work. For patients, reaching CR/sCR MRD negative timepoint earlier where MRD negative status is confirmed at earlier bone marrow evaluation, bone marrow aspiration and biopsy at end of study will be optional. Otherwise, all other bone marrow biopsies are mandatory.
h. After study therapy ends, follow-up will be 1 month after study end date. Patients may be followed at more frequent time intervals, and thereafter if clinically indicated. Patients who have progressive disease while on therapy will be followed with restaging scans and laboratory tests as clinically indicated. At disease progression, marrow and FDG-PET/CT are optional but recommended.
i. For patients with initial baseline 24-hr UPEP samples demonstrating ≥100 mg/24 hrs, patients will continue to have 24-hr UPEP samples day 1 of each cycle. Once 24-hr UPEP is <100 mg/24 hrs, patient can have random UPEP with IFE until achieving negativity. If initial baseline 24-hr UPEP sample is IFE positive and/or <100 mg/24 hrs, patients can have random UPEP samples with IFE until achieving negativity. Once random UPEP and IFE is negative, no further urine samples are needed (unless patient's disease is primarily measurable by 24 hr urines)
j. FDG-PET scan will be performed on patients at baseline, end of therapy (+/- 21 days) or upon suspicion of progressive disease as clinically indicated.
k. Variations of +/- 7 days of scheduled visits are permitted.
l. An echocardiogram (2-D or strain) will only be performed at baseline if the patient has had signs of significant cardiovascular disease. Outside echocardiograms are permissible.
m. If screening labs are performed within 5 days of C1D1 they can be used for treatment on day 1.
n. Variations of +/-21 days of scheduled visits are permitted.
o. Bone Marrow biopsy and aspirate will be required at time of serologic complete response. If patient is MRD negative on this bone

marrow one does not need to be completed at the end of treatment

Timepoints and potential analyses are listed below:

Bone Marrow

Sampling Time Points of Bone Marrow correlative studies

a) Baseline
b) End of therapy

*Patients undergoing MRD evaluation or End of study evaluation, the first pulled sample will be sent for Multiparametric flow cytometry and NGS MRD evaluation.

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

Bone Marrow Aspirate/Biopsy

Pathology/Immunohistochemistry

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

Minimal Residual Disease

Flow cytometry: Immunophenotyping of aberrant plasma cells by flow cytometry currently involves, but is not limited to, the use of the following reagents: CD138, CD19, CD45, CD38, and CD56. Characteristic changes in immunophenotypically abnormal plasma cells (CD38 bright and/or CD138 positive) include but are not limited to decreased or absent CD19 and CD45, decreased CD38, increased CD56, decreased CD27, decreased CD81, increased CD117. The first pulled bone marrow sample will be sent for multi-parametric flow cytometry as a priority. Samples will undergo MRD testing per MSK institutional practice, see section 12.0 for further methodology practice.

Molecular pathology: For MRD samples utilizing the NGS ClonoSEQ™ V2.0 (Adaptive Biotechnologies Seattle, WA) platform, immunoglobulin heavy and kappa chain variable, diversity, and joining gene segments from genomic DNA obtained from CD138+ bone marrow (BM) cell lysate or cell-free supernatant BM aspirate were amplified using universal primer sets as described elsewhere[21]. An MM clonotype was defined as an immunoglobulin rearrangement identified by NGS at a frequency of ≥5%.

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

FISH and cytogenetics

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

DNA-based target mutations

Bone marrow aspirate samples will be analyzed for somatic mutations by exome-sequencing of targeted genes using MSKCC MyType assay.

Cell Sorting and Bone marrow cell lysate

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

Research Blood/Serum and Urine

a) One 7-8 mL serum tube will be collected on Day 1, Day 8, Day 15, and Day 22 of Cycle 1 and 2, Day 1 of every cycle during cycles 3-6, if and when **CR/sCR** is achieved, at the end of therapy, and at any time point if the patient has progression of disease. One 7-8 mL CPT tube will be collected on Day 1 of every cycle during cycles 1-6, if and when **CR/sCR** is achieved, at the end of therapy, and at any time point if the patient has progression of disease.
b) Urine (random samples of 10 mL) will be collected into a standard urine collection cup and sent for analysis and storage at each of the above time points.

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

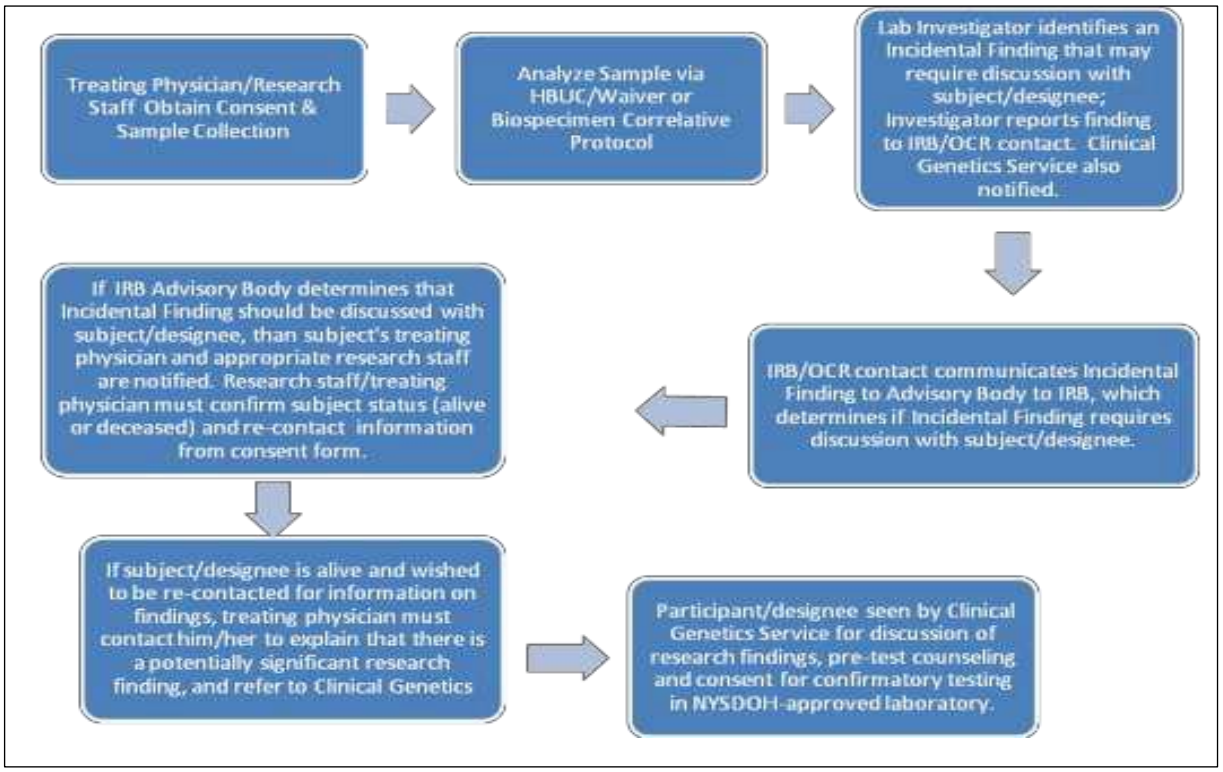
Assessment/Evaluation Plan

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

In the event an investigator's research identifies a finding that he or she believes should be communicated to the subject (and/or family designee), the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

After appropriate counseling and consent, the Clinical Genetics Service will request permission to confirm the result in a New York DOH-approved laboratory prior to communication of the specific result. If the patient is not available (e.g. deceased), then the surrogate designated on the consent will be contacted and the above will occur.

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



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

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

Contact: ocrgapirb@mskcc.org

11.1 TOXICITIES/SIDE EFFECTS

11.1 Daratumumab

Infusion Related Reactions

Daratumumab is an antibody. An antibody is a large protein that is used by the immune system to identify and neutralize bacteria and viruses. A side effect to daratumumab that occurs during or shortly after an infusion is completed (when the medicine is given into a vein) is called an infusion-related reaction. Infusion–related reactions were reported in approximately half of all patients treated with daratumumab. It usually occurs with the first infusion and during or within the first few hours of the start of the infusion. Signs and symptoms of infusion-related reactions may include respiratory symptoms, such as stuffy nose, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms are having trouble breathing (wheezing), runny nose, fever, chest discomfort, itching of the skin, and low blood pressure or high blood pressure. Most of the observed infusion-related reactions so far were mild or moderate, and ended by temporarily stopping the infusion and giving medicines to treat the side effect. Tell your doctor right away if you have above mentioned symptoms.

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

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

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

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

- You will get medications, including steroids, acetaminophen and antihistamine, before the infusion.
- If you have a reaction, the infusion will be paused and the symptoms treated as needed. Dependent on the reaction, the infusion may continue at a slower rate. If you have a life-threatening reaction, you will need to stop further treatment with daratumumab and your doctor will discuss alternative treatments with you.

- If you are considered higher risk for breathing problems (for example COPD, asthma), you may also get medications, including inhaled steroids, after the infusion.
- You may stay overnight in hospital after the infusion so medical staff can check you.

Possible Side Effects of Daratumumab

Among the 151 subjects treated with 16 mg/kg daratumumab as monotherapy in Studies GEN501 and MMY2002, the most frequently reported AEs (reported in >10% of subjects) were fatigue (29%); anemia (23%); nausea (19%); back pain (18%); cough (17%); thrombocytopenia (16%); decreased appetite (13%); pyrexia, dyspnea, upper respiratory tract infection (12% each); nasal congestion and neutropenia (11% each). Grade 3 and higher AEs were reported in 48% of subjects treated with 16 mg/kg monotherapy daratumumab. The most frequently reported Grade 3 or higher AEs were anemia (13%) and thrombocytopenia (9%). All other Grade 3 and higher AEs were reported in <5% of subjects. No deaths due to daratumumab-related AEs have been reported in any ongoing study.

Among the 283 patients who received daratumumab in combination with lenalidomide and dexamethasone in the POLLUX trial[12], please see Table 7 and Table 8 (DRd (N=283) %) for the most frequently reported AEs (reported in >10% of subjects) and the most frequently reported Grade 3 or higher AEs. All other Grade 3 and higher AEs were reported in <5% of subjects.

Table 7: Adverse reactions reported in ≥ 10% of patients and with at least a 5% greater frequency in the DRd arm in POLLUX

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

Table 8: Treatment-emergent hematology laboratory abnormalities in POLLUX

	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any 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.

Indirect Antiglobulin Testing

Daratumumab treatment will affect one of these tests known as an indirect antiglobulin test (IAT; also known as an indirect Coombs test). Therefore, an IAT will be done before receiving daratumumab.

Birth control and pregnancy during the study

The effects of daratumumab on fertility, the human embryo, the fetus, or the breast-fed infant are unknown. Both male and female patients must use effective methods of birth control during the course of the study and for 3 months after stopping daratumumab. Women must not donate eggs during the study and for 3 months after your last dose of study drug. Men must not donate sperm during the study and for 3 months after your last dose of study drug.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Disease Parameters

Minimal Residual Disease

For patients undergoing MRD or end of study assessment, the first pulled bone marrow sample will be sent for multi-parametric flow cytometry as a priority. Flow cytometry based assay to rule out MRD in bone marrow aspirates and for MRD negative status using an assay with a sensitivity of at least 1 in 10 ^ -5 cells. Patients with <CR/sCR are considered MRD positive. We will use the MSKCC flow cytometry MRD method which is based on 10-colors in a single tube.[16]. The test demonstrates highly similar results when compared to the current Euroflow approach. This test is validated and already in clinical use at MSK. Immunophenotyping of aberrant plasma cells by flow cytometry currently involves, but is not limited to, the use of the following reagents: CD138, CD19, CD45, CD38, and CD56. Characteristic changes in immunophenotypically abnormal plasma cells (CD38 bright and/or CD138 positive)
include but are not limited to decreased or absent CD19 and CD45, decreased CD38, increased CD56, decreased CD27, decreased CD81, increased CD117.

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

Evaluation of Response Criteria

a) Stringent Complete Response (sCR)
    - Complete Response as defined below plus: Normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence (presence/ absence of clonal cells is based on the kappa/ lambda ratio.

b) Complete Response (CR)

- Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <= 5% plasma cells in bone marrow

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

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

e) Stable Disease (SD)
   - Not meeting criteria for CR, VGPR, PR or progressive disease. All categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

f) Progressive disease (PD)
   - Requires any one or more of the following:
     - Increase of ≥ 25% of nadir in:
     - Serum M-component and/or (absolute increase must be ≥ 0.5 g/dl. The serum M-component increases of ≥ 1gm/dl are sufficient to define relapse if starting M-component is ≥ 5 gm/dl.
     - Urine M-component and/or (the absolute increase must be ≥ 200 mg/24h
     - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10mg/dl.
     - Bone marrow plasma cell percentage: the absolute % must be ≥ 10%
     - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas
     - Development of that can be attributed solely to the plasma cell proliferative disorder

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

bone lesion, hypercalcemia

Progression-Free Survival

PFS is defined as time of start of treatment to time of progression or death, whichever occurs first. Patients alive and progression-free at the end of study will be censored at that time.

Overall Survival

Overall survival is defined as the time of start of treatment to death from any cause. Patients alive at the end of study will be censored at that time.

Toxicity Criteria

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

13.1 CRITERIA FOR REMOVAL FROM STUDY

Off-therapy Criteria

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

- Hematologic toxicity has not completely resolved or resolved to < grade 1 or baseline after 2 weeks of withholding treatment
- Therapy has been held for more than 3 weeks due to grade 3 or higher non-hematologic toxicity
- Patient completes the protocol treatment
- Progression of disease
- Patient chooses to go off therapy
- The principal investigator may remove patient from protocol therapy if deemed necessary due to medical conditions, compliance, etc.
- Patient becomes pregnant.

Off-Study Criteria

- Patient requests to be withdrawn from study
- Death
- Physician's determination that withdrawal is in the patient's best interest.
- Patient who have gone on to other treatments aside from revlimid

maintenance (5-15 mg daily 21-28/ 28-day cycle)

14.1 BIOSTATISTICS

Study Design/Primary Endpoints

This is a single arm phase II study designed to evaluate the efficacy of short course therapy with daratumumab, in multiple myeloma patients achieving a VGPR or better with MRD positive state while on lenalidomide maintenance for at least 6 months at the time of enrollment. The primary objective of this study is to determine the rate of conversion to MRD negativity by the completion of 6 cycles of treatment.

Rationale

The primary objective of this trial is to determine whether treatment with daratumumab is associated with a substantial fraction of patients with MRD positive multiple myeloma converting to a MRD negative state as assessed by multicolor flow cytometry. Previously studies have reported that approximately 10% of patients will achieve deeper responses including MRD negativity after maintenance therapy with lenalidomide alone[18]. The current study will be considered positive if the rate of MRD negativity is 30% or higher with daratumumab.

Power Calculations

This study will implement a Simon's two-stage minimax design to distinguish between an unpromising rate of 10% and a promising rate of 30%. The study is designed to have a type I error and a type II error of 0.10. The maximum sample size is 25 patients.

Primary analysis

In the first stage of the study, a total of 16 patients will accrue. If 2 or more patients achieve MRD negativity, additional 9 patients will accrue. If at the end of the study, 5 patients or more out the total 25 patients achieve MRD negativity, the short course daratumumab will be considered promising for future investigation.

Accrual will be held after the 16th patient if 2 or more patients have not yet achieved MRD negativity. We anticipate that one to two patients will accrue each month.

Analysis population for primary endpoint

All patients who receive at least one dose of daratumumab will be considered evaluable for the primary endpoint. Patients who do not have the end of therapy bone marrow for any reason and have not achieved MRD negativity at any point while on study will be considered a treatment failure.

Secondary endpoints:

1. To estimate the rate of sustained MRD negativity. Among patients achieving MRD negativity, sustained negativity is defined as remaining MRD negative at the 1-year post treatment

completion bone marrow biopsy. The proportion along with the 95% confidence interval will be estimated.

2. Kaplan-Meier methodology will be used to estimate the duration of MRD negativity. This endpoint is defined as the time from MRD negativity achievement to MRD positivity, progression of disease, or death. The median along with the corresponding 95% confidence interval will be estimated.

3. To explore the concordance of different MRD methodologies. MRD status by multiparametric flow cytometry will be compared to next-generation sequencing and to mass spectrometry based proteomics methodologies. The kappa statistic will be reported.

4. Kaplan-Meier methodology will be used to estimate progression-free survival and overall survival. Estimates of survival along with 95% confidence intervals will be provided for select time points.

Exploratory Studies:

1. The gene panel MyType (or alternative equivalent platform) will explore whether any mutations appear to be associated with the achievement of MRD negativity. This analysis is for hypothesis-generation, and all results will be cautiously interpreted. Fisher's exact test may be used to assess any potential association. The variant allele frequency (VAF) will be summarized for each mutation. VAFs will be adjusted for the cancer cell fraction. All results will be adjusted for multiple comparisons.

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

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study.

Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

This study will not include randomization.

16.1 DATA MANAGEMENT ISSUES

All patients will be enrolled on protocol at Memorial Sloan-Kettering Cancer Center. We expect to be able to enroll the necessary 25 patients into this study in 2 years.

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

The CRC will collect toxicity and concomitant medication information and patient interviews. Adverse events, including all toxic effects of treatment will be tabulated individually according to severity or toxicity grade. The data manager will also monitor laboratory testing throughout the study. Laboratory data will be tabulated and summarized by descriptive statistics, as well as on the basis of MSKCC specified normal ranges.

16.2 Quality Assurance

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

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

16.3 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical

trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.1 PROTECTION OF HUMAN SUBJECTS

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

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

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

17.2 Privacy

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

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

Health, and may be made accessible to investigators approved by the U.S. government.

Consent for re-contact

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

Use of identifiable information for genetic studies

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

If in the course of this research a research finding is obtained that may be critical to the preventive care of the participant or their family, as determined by procedures overseen by the IRB, those participants, if they consent to checklist questions 1, 2, will be referred to the Clinical Genetics Service for a consultation. At that time, genetic counseling can be offered in accordance with New York State requirements, and appropriate clinical testing offered in an approved laboratory. Please see flow chart and requirements for reporting under section 10.0.

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

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

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

Future use of samples

Researchers at MSKCC may either keep indefinitely or dispose of any specimen(s) collected

under this protocol including DNA that the samples contain. Specimens will be stored with identifiers in secure banks at MSKCC. Samples could be lost or ruined because of mechanical failure, and MSKCC cannot guarantee that samples will be stored indefinitely. The samples will be stored for as long as deemed useful for research purposes.

Risks of research participation

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

Benefits of research participation

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

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

Costs/compensation

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

17.3 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient of participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

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

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

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

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

The report should contain the following information:

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

17.2.1

AE/SAE Reporting by Investigator-sponsor to Janssen

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

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

This Study has been designated as an interventional study. As such, all adverse events for daratumumab regardless of causality and special situations excluding those from subjects not exposed to a J&JMedicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a subject has

signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

Adverse Event (AE) Definition:

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

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

Adverse Event of Special Interest Definition:

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

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

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

Individual Case Safety Report (ICSR) Definition:

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

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

The minimum information required is:

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

Product Quality Complaint (PQC)

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

Examples of PQC include but not limited to:

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

Serious Adverse Event (SAE)

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

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

- Is medically important*

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

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

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

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

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

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

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

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

Special Reporting Situations

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

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

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

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

Pregnancy

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

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

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

Maintenance of Safety Information

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

request.

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

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

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

SAEs and Special Reporting Situations

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

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

The PRINCIPAL INVESTIGATOR will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 10,Transmission Methods, in English by the next business day after becoming knowledgeable of the event

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

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

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

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

- Copies of any and all relevant correspondences with regulatory authorities and ethics

committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in Section 10 from this Exhibit by the next business day after such a report or correspondence being sent to the applicable health authorities.

Non-Seriou s AEs

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

PQC Reporting

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

All initial PQCs involving a J&J medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the PRINCIPAL INVESTIGATOR by the next business day after becoming knowledgeable of the event The Janssen contact will provide additional information/form to be completed.

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

Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-J&JMedicinal Products

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

Transmission Methods

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

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

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

18.1 INFORMED CONSENT PROCEDURES

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

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

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

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

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20.0 APPENDICES

Appendix A

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