Phase II study of daratumumab based response adapted therapy for older adults with newly diagnosed multiple myeloma

Protocol Number: 20130

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Sponsor Institution	**H. Lee Moffitt Cancer Center & Research Institute**
IND/IDE Sponsor/IND number	**144902**
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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Supporting Agency Terms. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed of their obligation to meet the above commitments.

Principal Investigator: _____
Rachid Baz, M.D.

Signed: _____ Date:_____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Phase II study of daratumumab based response adapted therapy for older adults with newly diagnosed multiple myeloma

Study Description: In this response adapted approach, older adults with newly diagnosed symptomatic multiple myeloma will receive daratumumab and dexamethasone for 2 months. Patients who achieve a partial response or better will continue on daratumumab. Patients who achieve less than a partial response will have lenalidomide or bortezomib added to their therapy. Patients who experience progressive disease on daratumumab after the initial 2 months of monotherapy or on the combination of daratumumab and either lenalidomide or bortezomib will come off study.

Objectives:

Primary Objective:

1- Efficacy of this response adapted approach in older adults with newly diagnosed myeloma

Secondary Objectives:

1- Safety profile of daratumumab based therapy in older adults with newly diagnosed myeloma
2- Identification of potential biomarkers for the prediction of response

Endpoints:

Primary Endpoint: Best response per the IMWG Uniform response criteria for the response adapted approach (partial response (PR) or better) based on investigator assessment

Secondary Endpoints:

1- The 1 and 2 years progression free survival (PFS) of the study population
2- Overall response rate (partial response or better) after 2 cycles of daratumumab
3- Proportion of patients who continue on daratumumab monotherapy after 2 cycles.
4- Proportion of patients who are without minimal residual disease (MRD-) using Next Generation sequencing (NGS)
5- The 2 year overall survival of this response adapted approach
6- Safety profile of subcutaneous daratumumab based therapy in older adults newly diagnosed multiple myeloma
7- Agreement between actual responses and responses as predicted by an Ex Vivo Mathematical Myeloma Advisor (EMMA)

Exploratory endpoints/ correlative:

1- Immune profiling at baseline and after daratumumab dexamethasone for newly diagnosed myeloma.

2- Validate EMMA in silico predictions of daratumumab response.
3- Incorporate clinical parameters and early dynamics of monoclonal paraprotein response to therapy to extend EMMA's capacity to include longer term predictions of patient outcomes.
4- Correlation between a simplified geriatric assessment (frailty) and grade 3 and 4 (hematologic and non-hematologic) toxicity from therapy as well as discontinuation due to adverse events
5- Evaluation potential molecular biomarkers of clinical response to trial associated therapy.

Study Population: **Eligible patients:**

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Understand and voluntarily sign an informed consent form.

2. Age ≥65 years and presence of coexisting conditions which in the opinion of the treating physician are likely to result in the development of unacceptable side effects associated with high-dose chemotherapy with stem-cell transplantation

3. Able to adhere to the study visit schedule and other protocol requirements.

4. Diagnosed with multiple myeloma and be considered to have active disease with either CRAB criteria or myeloma defining events (bone marrow ≥ 60% plasma cells, sFLC ratio≥ 100 or MRI or PET defined lesions) (Appendix C). Patients must not have received an active chemotherapy regimen. Patients may have received palliative radiotherapy at least 2 weeks prior to the study start. Dexamethasone up to 160 mg total dose is allowed prior to participation

5. Measurable myeloma paraprotein levels in serum (≥ 0.5 g/dL), urine (≥ 0.2 g excreted in a 24-hour urine collection sample) or by serum free light chains (involved free light chain greater than 100mg/L)

6. Eastern Cooperative Group (ECOG) Performance Status of 0 - 2.

7. Serum bilirubin levels ≤1.5 times the upper limit of the normal range for the laboratory (ULN).

8. Serum AST or serum ALT] levels ≤2 x ULN

9. Must have adequate bone marrow function:

    a. Absolute neutrophil count $\geq$ 1,000 cells/mm^3 (1.0 x 10^9/L).

    b. Platelets ≥ 75,000 /mm^3.

10. Hemoglobin > 8 g/dL (transfusions are allowed)

11. Calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula.

12. Men must agree to use a latex condom during sexual contact with a female of child bearing potential even if they have had a successful vasectomy. See Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Exclusion criteria

The presence of any of the following will exclude a subject from study enrollment:

1. Ongoing severe infection requiring intravenous antibiotic treatment.

2. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in-situ cervical cancer, or other cancer from which the subject has been disease-free for at least 2 years.

3. Solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia.

4. Patients with known COPD with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal and , moderate or severe persistent asthma within the past 2 years or uncontrolled asthma. Patients with a history of COPD will have pulmonary function testing to include FEV1

5. Uncontrolled medical problems such as diabetes mellitus, congestive heart failure, coronary artery disease, hypertension, unstable angina, arrhythmias), pulmonary, hepatic and renal diseases unless renal insufficiency is felt to be secondary to multiple myeloma.

6. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

7. Pregnant or lactating females.

8. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

9. Concurrent use of other anti-cancer agents or treatments with the exception for hormonal therapy which is allowed.

10. Known allergy or hypersensititvity or intolerance to any of the study drugs, hyaluronidase, mAbs, human proteins, or their excipients (refer to daratumumab IB), or known sensitivity to mammalian-derived products

11. Seropositive for human immunodeficiency virus (HIV)

12. 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.

13. 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).

Phase: Phase II, open label

Description of Sites/Facilities Enrolling Participants: H. Lee Moffitt Cancer Center & Research Institute

Description of Study Intervention: Patient will receive daratumumab (1800 mg in 15 ml) premixed with recombinant human hyaluronidase enzyme (rHuPH20 30,000 units) to be administered by manual subcutaneous injections over 3-5 minutes on the following schedule: weekly for the first 8 injections

In the event of a partial response or better, patient will continue on arm A and receive SC daratumumab every 2 weeks for the next 8 injections and monthly thereafter. Supportive medicine including antihistamine acetaminophen, and corticosteroids will be per standard of care premedications for daratumumab. On the weeks when the patient is not to receive daratumumab, dexamethasone 20 mg PO will be given only.

In the event of less than a partial response (stable disease, minimal response or progressive disease) after 2 cycles, lenalidomide or bortezomib will be added. The decision to use bortezomib or lenalidomide will be at the discretion of the treating physician (based on which agent is expected to be better tolerated), the patient preference and informed by EMMA (after a repeat bone marrow aspiration)

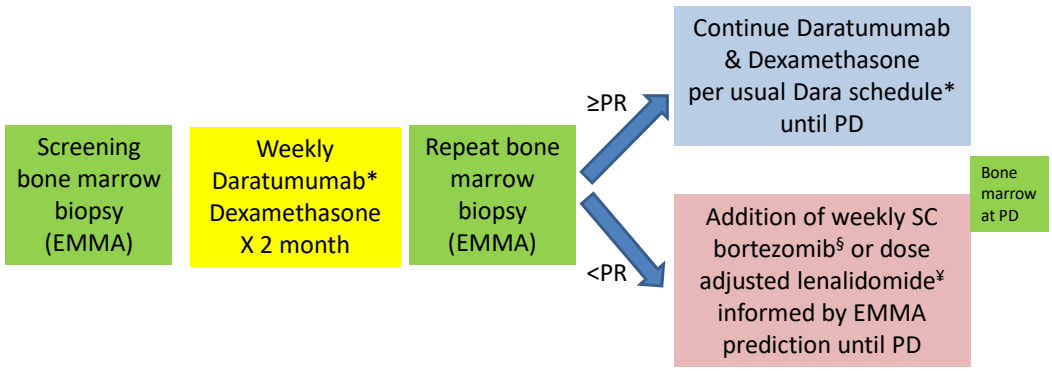
If lenalidomide is to be added to daratumumab (arm B), lenalidomide will be used at a starting dose of 10-25 mg PO D1-21 every 28 days. The starting dose of lenalidomide will be 10 mg if the creatinine clearance is < 50 ml/min or the patient is over 80 years of age, 15 mg if the patient is 75 years of age or older and the creatinine clearance is >50 ml/min; and 25 mg if the patient is <75 years and with a creatinine clearance of 50 ml/min. During the first 4 cycles of lenalidomide, daratumumab will be given every 2 weeks and after the first 4 cycles of lenalidomide, daratumumab will be administered every month. On the weeks when the patient is not to receive daratumumab, dexamethasone 20 mg PO will be given.

If bortezomib is to be added to daratumumab and dexamethasone, patients will receive weekly SC bortezomib at a starting dose of 1.3 mg/m2 on days 1,8,15 every 28 days in combination with daratumumab every 2 weeks for

	the next 4 cycles (each cycle is 28 days) and then monthly daratumumab after. On the weeks when the patient is not to receive daratumumab, dexamethasone 20 mg PO will be given (figure 2). After 8 cycles of bortezomib based therapy (cycle 10 of the trial), patients may receive a less frequent maintenance dose of bortezomib (including discontinue bortezomib) at the discretion of the treating physician. Treatment will be continued until progressive disease. Commercial supply of lenalidomide and bortezomib will be used for this study.
Study Duration:	It is estimated that accrual will be completed in 2 years. In that case the data would need another year to mature.
Participant Duration:	Treatment will be continued until progressive disease or unacceptable toxicity. The estimated median PFS for newly diagnosed older adults with multiple myeloma was 25 months in a study of lenalidomide and dexamethasone

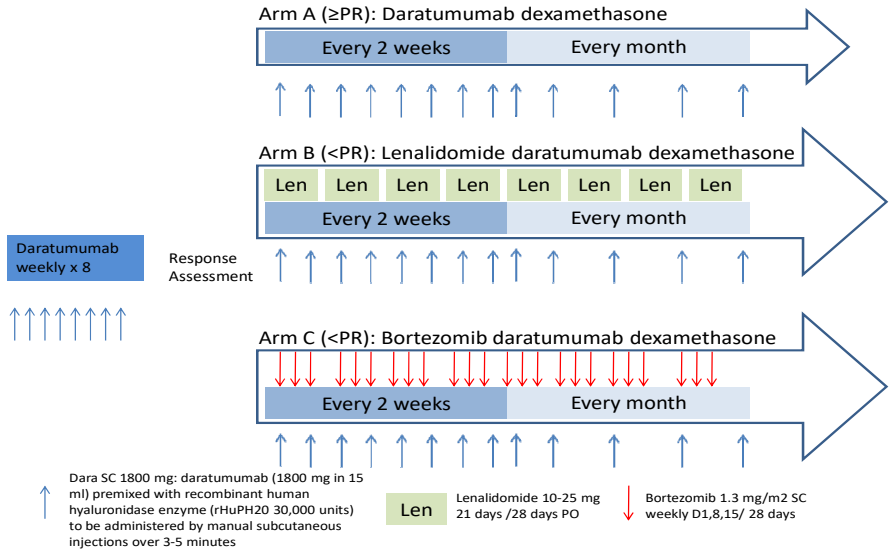
1.2 SCHEMA

Treatment / Study Schema



* Daratumumab SC weekly x 8, then every 2 weeks x 8 and then monthly. Dexamethasone 20 mg weekly starting dose)

§ Bortezomib 1.3 mg/m2 SC D1,8,15/28 days
¥ Lenalidomide 10-25 mg PO D1-21/28 days (dosing based on frailty / CrCl)
Bortezomib and lenalidomide based therapy per standard of care, administration could be done at local oncologist office (given safety of combination per CASTOR and POLLUX). All Daratumumab to be administered at MCC given study drug.
PD: progression of disease; EMMA: *Ex Vivo* Mathematical Myeloma Advisor (CLIA based), PR: Partial Response



After 8 cycles of bortezomib based therapy (cycle 10 of the trial), patients may receive a less frequent maintenance dose of bortezomib (including discontinue bortezomib) at the discretion of the treating physician.

1.3 SCHEDULE OF ACTIVITIES (SOA)

The following assessment will be performed for safety but not collected on electronic case report forms after the baseline / screening evaluation (abnormalities / adverse events noted in the assessments below however will be collected on the AE log): vital signs, hematology, serum chemistry, concomitant medication review, pregnancy tests when applicable, height and weight.

Arm A

Procedures	Screening Day -28 to -1	Enrollment/Baseline Cycle 1 Day 1	Cycle 1 Days 8, 15, 22 +/-1 day	Cycle 2 Day1 Day 28 +/- 1 day	Cycle 2 Days 8,15 +/-1 day	Cycle 2 Day 22 +/- 1 day	Cycles 3,4,5,6 Days 1 Every 28 days +/-7 day	Cycle 3,4,5,6 Days 15 +/-4 day	Cycle 7+ Day 1 Every 28 days +/-7 day	End of study +/-28 days
Informed consent	X									
Demographics	X									
Medical history	X									
Myeloma Response Assessment [a]	X	x		x		x	x		x	x
Bone marrow biopsy / aspirate [b]	X					x				x
B2 microglobulin	X									
Administer SC daratumumab		X	X	X	X	X	X	X	X	
Dexamethasone		X	X	X	X	X	X	X	X	
Concomitant medication review	X	X----------							----------X	
Physical exam	X	X		X			X		X	X
Vital signs	X	X		X			X		X	X
Height	X									
Weight	X	X		X			X			X
ECOG Performance status	X	X		X			X		X	X
Hematology	X[g]	X	X	X	X	X	X	X	X	X
Serum chemistry [c]	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C and HIV	X									
Geriatric Assessment[d]	X					X				
Adverse event review and evaluation	X	X----------							----------X	X
Bone survey or PET CT[e]	X									X
Immune Profiling [f]	X					X				
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X

a: Serum protein electrophoresis, serum immunofixation, 24 h urine electrophoresis and immunofixation, serum free light chains. The 24 h urine protein electrophoresis does not need to be repeated on cycle 1 day 1 if performed within 7 days of that date as part of screening.

b: Bone marrow biopsy at screening to include cytogenetics, FISH and for identification of a possible future MRD clone. EMMA assay to be performed on bone marrow aspirate sample obtained on screening and cycle 2 Day 22. In addition, bone marrow biopsy and aspirate will be performed in patients with VGPR or CR for MRD assessment and determination of CR (for VGPR, if the remainder M spike is consistent with daratumumab interference)

c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, AST, ALT, sodium.

d: Geriatric assessment will include the IMWG geriatric assessment as well as a modified Balducci and testing for CRP and D- Dimer

e: If PET CT or bone survery has been performed within 28 days of cycle 1 day 1 but prior to screening (per standard of care) , it would not need to be repeated during screening

f: Immune profiling to be performed at screening and on cycle 2 day 22

g: A type and screen will be performed on screening only

Arm B

Procedures	Screening Day -28 to -1	Enrollment/Baseline Cycle 1 Day 1	Cycle 1 Days 8, 15, 22 +/-1 day	Cycle 2 Day1 Day 28 +/- 1 day	Cycle 2 Days 8,15 +/-1 day	Cycle 2 Day 22 +/- 1 day	Cycles 3,4,5,6 Days 1 Every 28 days +/-7 day	Cycle 3,4,5,6 Days 15 +/-4 days	Cycle 7+ Day 1 Every 28 days +/-7 day	End of study +/- 28 days
Informed consent	X									
Demographics	X									
Medical history	X									
Myeloma Response Assessment [a]	X	x		x		x	x		x	x
Bone marrow biopsy / aspirate [b]	X					x				x
B2 microglobulin	X									
Administer SC daratumumab		X	X	X	X	X	X	X	X	
Lenalidomide [c]							X	X	X	
Dexamethasone		X	X	X	X	X	X	X	X	
Concomitant medication review	X	X----------							X	
Physical exam	X	X		X			X		X	X
Collect diary				X			X		X	X
Vital signs	X	X		X			X		X	X
Height	X									
Weight	X	X		X			X		X	X
ECOG Performance status	X	X		X			X		X	X
Hematology	X[h]	X	X	X	X	X	X	X	X	X
serum chemistry [d]	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C and HIV	X									
Geriatric Assessment[e]	X					X				
Adverse event review and evaluation	X	X----------							X	X
Bone survey or PET CT[f]	X									X
Immune Profiling [g]	X					X				
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X

a: Serum protein electrophoresis, serum immunofixation, 24 h urine electrophoresis and immunofixation, serum free light chains. The 24 h urine protein electrophoresis does not need to be repeated on cycle 1 day 1 if performed within 7 days of that date as part of screening.

b: Bone marrow biopsy at screening to include cytogenetics, FISH and for identification of a possible future MRD clone. EMMA assay to be performed on bone marrow aspirate sample obtained on screening and cycle 2 Day 22. In addition, bone marrow biopsy and aspirate will be performed in patients with VGPR or CR for MRD assessment and determination of CR (for VGPR, if the remainder M spike is consistent with daratumumab interference)

c: Patients will take lenalidomide orally on D1-21 every 28 days cycle

d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, AST, ALT, sodium.

e: Geriatric assessment will include the IMWG geriatric assessment as well as a modified Balducci and testing for CRP and D- Dimer

f: If PET CT or bone survery has been performed within 28 days of cycle 1 day 1 but prior to screening (per standard of care) , it would not need to be repeated during screening.

g: Immune profiling to be performed at screening and on cycle 2 day 22

h: A type and screen will be performed on screening only

Arm C

Procedures	Screening Day -28 to -1	Enrollment/Baseline Cycle 1 Day 1	Cycle 1 Days 8, 15, 22 +/-1 day	Cycle 2 Day1 Day 28 +/- 1 day	Cycle 2 Days 8,15 +/-1 day	Cycle 2 Day 22 +/- 1 day	Cycles 3,4,5,6 Days 1 Every 28 days +/-7 day	Cycle 3,4,5,6 Day 8 +/-2 days	Cycle 3,4,5,6 Days 15 +/-2 days	Cycle 7+ Day 1 Every 28 days +/-7 days	Cycle 7+ Day 8,15 Every 28 days +/-2 days	End of study +/- 28 days
Informed consent	X											
Demographics	X											
Medical history	X											
Myeloma Response Assessment [a]	X	X		X		X	X			X		x
Bone marrow biopsy / aspirate [b]	X					x						x
B2 microglobulin	X											
Administer SC daratumumab		X	X	X	X	X	X		X	X		
Administer SC bortezomib [c]							X	X	X	X	X	
Dexamethasone		X	X	X	X	X	X		X	X	X	
Concomitant medication review	X	X----------									----------X	
Physical exam	X	X		X			X			X		X
Vital signs	X	X		X			X			X		X
Height	X											
Weight	X	X		X			X			X		X
ECOG Performance status	X	X		X			X			X		X
Hematology	X[h]	X	X	X	X	X	X			X		X
serum chemistry [d]	X	X	X	X	X	X	X			X		X
Hepatitis B and C and HIV	X											
Geriatric Assessment[e]	X					X						
Adverse event review and evaluation	X	X----------									----------X	X
Bone survey or PET CT[f]	X											X
Immune Profiling [g]	X					X						
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X		X	X		X

a: Serum protein electrophoresis, serum immunofixation, 24 h urine electrophoresis and immunofixation, serum free light chains. The 24 h urine protein electrophoresis does not need to be repeated on cycle 1 day 1 if performed within 7 days of that date as part of screening.

b: Bone marrow biopsy at screening to include cytogenetics, FISH and for identification of a possible future MRD clone. EMMA assay to be performed on bone marrow aspirate sample obtained on screening and cycle 2 Day 22. In addition, bone marrow biopsy and aspirate will be performed in patients with VGPR or CR for MRD assessment and determination of CR (for VGPR, if the remainder M spike is consistent with daratumumab interference)

c: Bortezomib will be administered at a starting dose of 1.3 mg/m2 SC D1,8,15 every 28 days cycle. After 8 cycles of bortezomib based therapy (cycle 10 of the trial), patients may receive a less frequent maintenance dose of bortezomib (including discontinue bortezomib) at the discretion of the treating physician.

d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, AST, ALT, sodium.

e: Geriatric assessment will include the IMWG geriatric assessment as well as a modified Balducci and testing for CRP and D- Dimer

f: If PET CT or bone survery has been performed within 28 days of cycle 1 day 1 but prior to screening (per standard of care) , it would not need to be repeated during screening

g: Immune profiling to be performed at screening and on cycle 2 day 22

h: A type and screen will be performed on screening only

INTRODUCTION

1.4 STUDY RATIONALE

The median age of diagnosis of patients with multiple myeloma is about 70 years of age and only about 1/3 of myeloma patients at tertiary care centers receive high dose therapy and bone marrow transplantation. Despite the availability of novel agents, the outcome of older adults with multiple myeloma remains suboptimal and little improvements have been noted. Of particular note, several groups have evaluated a geriatric assessment of frailty in older adults with multiple myeloma and this assessment was one of the most powerful predictors of outcomes (as well as non-hematologic toxicity and discontinuation of therapy) for patients treated with immunomodulatory agents, proteasome inhibitors with or without alkylating agents[1-3].

The FIRST and UPFRONT trials have solidified lenalidomide and dexamethasone or bortezomib and dexamethasone respectively as the treatment of choice for first line therapy in older adults with myeloma[4, 5]. Specifically in this patient population, the FIRST trial demonstrated superiority of continuous lenalidomide dexamethasone versus the combination of melphalan prednisone and thalidomide or a fixed duration (18 months) of lenalidomide dexamethasone[4]. The median PFS for lenalidomide and dexamethasone was 25.5 months and 59% of patients were alive at 4 years. The overall response rate of lenalidomide and dexamethasone was 75% with 15% of patients achieving a complete response[4]. The UPFRONT trial demonstrated similar outcomes with bortezomib dexamethasone versus bortezomib dexamethasone and melphalan or bortezomib dexamethasone and thalidomide although the doublet was associated with less adverse events[5]. In that trial, bortezomib dexamethasone resulted in a median PFS of 14.7 months and a median overall survival of 49.8 months. The overall response rate of bortezomib and dexamethasone was 73% and 3% of patients achieved a complete response[5].

Daratumumab is a human IgG kappa CD38 directed monoclonal antibody with multiple mechanisms of actions including direct antitumor effects and immunomodulatory effects resulting in the depletion of immunosuppressive cells and expansion of cytotoxic T cells . It results in a response rate of 30% in heavily pretreated myeloma patients and a response rate of about 50% in patients with smoldering myeloma[6]. Daratumumab was recently approved by the US FDA for the treatment of newly diagnosed multiple myeloma in combination with bortezomib melphalan and prednisone based on the ALCYONE trial comparing this therapy to bortezomib melphalan and prednisone[7]. In that trial daratumumab and bortezomib melphalan and prednisone resulted in an overall response rate of 90.9% and a complete response rate of 42%. The median PFS was not reached at the time of this report but the 12 months PFS was 87%[7]. Importantly, aside of infusion-related reactions (IRR), daratumumab is well tolerated and has little related non hematologic toxicities[6-9]. Infusion reactions are noted usually in the first or second infusions and can be decreased by subcutaneous administration of daratumumab. In fact the PAVO study noted IRR in 12% of patients which compares favorably with about 40% noted with IV administration.[10] Importantly the infusion time can be shortened significantly with SC administration without impacting efficacy[10]. An ongoing phase III clinical trial is comparing SC and IV daratumumab in patients with relapsed and refractory multiple myeloma (clinicaltrials.gov NCT03277105). Daratumumab monotherapy has not been evaluated in newly diagnosed myeloma.

Given the mechanism of action of daratumumab and above safety data, we anticipate that this agent would be well tolerated by older adults with multiple myeloma and possibly would not be impacted by the frailty of the patients. Accordingly, we propose to evaluate a daratumumab based response adapted therapy for older adults with newly diagnosed symptomatic multiple myeloma. Specifically; eligible patients will receive 2 months of therapy with weekly SC daratumumab and dexamethasone. Patients who experience a partial response or better would continue on daratumumab and dexamethasone until progressive disease (every 2 weeks for 4 months and then monthly for daratumumab and weekly dexamethasone). For patients who experience less than a partial response, (MR, SD or PD);

lenalidomide or bortezomib would be added to their treatment regimen. The choice of additional therapy (bortezomib or lenalidomide) would be informed by an *Ex Vivo* Mathematical Myeloma Advisor (EMMA) and by a discussion between the treating physician and the patient. The safety and efficacy of the combination of bortezomib or lenalidomide with daratumumab has been established in the Castor and Pollux studies, respectively[8, 9]. Importantly subcutaneous delivery of daratumumab would reduce the infusion duration and potential for infusion related adverse events which would be particularly of benefit for older adults with multiple myeloma

1.5 BACKGROUND

1.5.1 DARATUMUMAB

1.5.1.1 Non clinical studies

In mouse xenograft models, daratumumab reduced tumor growth in both preventive and therapeutic settings. Daratumumab had no effect on proliferation of human peripheral blood mononuclear cells (PBMCs), and cytokine release was similar to other marketed therapeutic antibodies. Hence, daratumumab can recruit multiple effector mechanisms to facilitate the lysis of malignant cells in vitro and in vivo. In-vitro studies, using bone marrow mononuclear cells from patients with multiple myeloma (MM), demonstrated increased killing of tumor cells when daratumumab was combined with lenalidomide or bortezomib as well as with both lenalidomide and bortezomib. Additionally, the upregulation of CD38 by pomalidomide or lenalidomide can enhance the activity of anti-CD38 antibodies including daratumumab. These observations suggest a strong potential for the treatment of CD38-expressing malignancies using daratumumab as monotherapy and in combinations.

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

1.5.1.2 Clinical Studies

Daratumumab has being evaluated in multiple company sponsored clinical studies in subjects across the multiple myeloma disease continuum, ie, smoldering multiple myeloma, previously untreated multiple myeloma, relapsed/refractory multiple myeloma, and other diseases including myelodysplastic syndrome (MDS), lung cancer, natural killer (NK)/T-cell lymphoma and non-Hodgkin lymphoma. In addition, IV daratumumab is currently approved by the U.S. Food and Drug Administration for patients with untreated multiple myeloma as well as relapsed and refractory multiple myeloma. Over 2,700 subjects have been treated with daratumumab monotherapy or combination therapy in 14 clinical studies that contribute study-specific safety summaries to the current daratumumab Investigator Brochure (IB; version 17, dated 17 December 2020). Of these subjects, daratumumab has been administered to approximately 1,160 subjects as monotherapy in Studies GEN501, MMY1002, and MMY2002, SMM2001, LYM2001, MMY1004 (SC) and MMY3010. Daratumumab as combination therapy has been administered to approximately 1,533 subjects in Studies GEN503, MMY1001, MMY1005, MMY3003, MMY3004, MMY3007, and MMY3008.

Monotherapy studies in subjects with relapsed/refractory multiple myeloma are:

- GEN501, MMY1002, MMY1004, MMY2002, SMM2001, MMY3010

Combination therapy studies are:

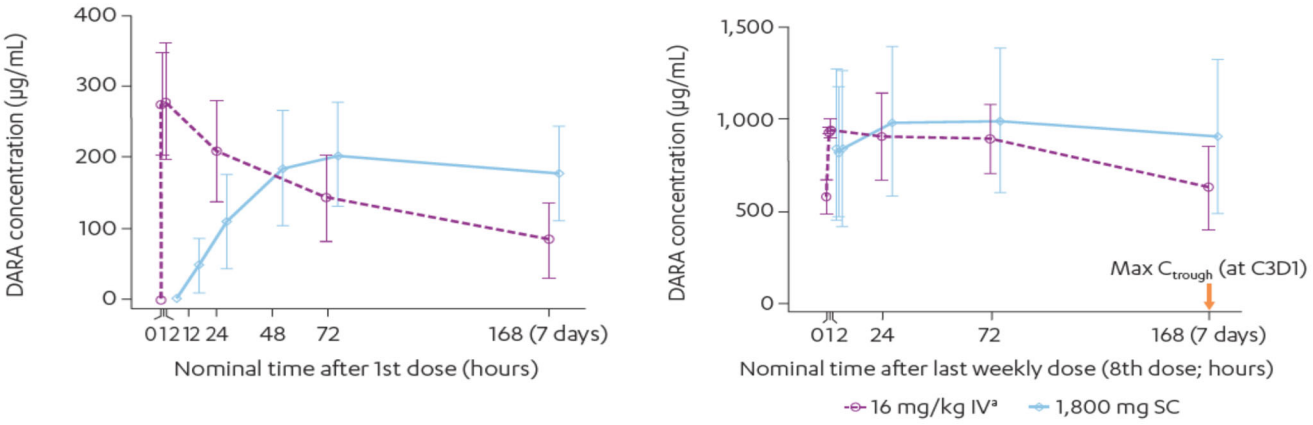
- Subjects with previously untreated and relapsed/refractory multiple myeloma:

- MMY1001: daratumumab in combination with bortezomib-dexamethasone (Vd), bortezomib-thalidomide-dexamethasone (VTd), bortezomib-melphalan-prednisone (VMP), carfilzomib-lenalidomide-dexamethasone [KRd] in subjects with previously untreated multiple myeloma and pomalidomide dexamethasone [Pomdex] and carfilzomib-dexamethasone [Kd])

- Subjects with relapsed/refractory multiple myeloma:
  - GEN503: daratumumab in combination with lenalidomide-dexamethasone (Rd)
  - MMY1005: daratumumab in combination with Vd (in Japan)
  - MMY3003: daratumumab in combination with Rd
  - MMY3004: daratumumab in combination with Vd
- Subjects with previously untreated multiple myeloma:
  - MMY3007: daratumumab in combination with VMP
  - MMY3008: daratumumab in combination with Rd
- Monotherapy Non-Hodgkin's Lymphoma
  - LYM2001

1.5.1.2.1 Pharmacokinetics

For IV daratumumab, over the dose range from 1 to 24 mg/kg as monotherapy or 1 to 16 mg/kg in combination with other treatments, increases in area under the curve (AUC) were more than dose-proportional. Clearance was rapid at low doses and slower at higher doses; clearance also decreased with multiple doses. This PK profile was consistent with target-mediated disposition indicating target saturation at higher doses. The PK of daratumumab was similar following monotherapy and combination therapies in multiple myeloma. The mean ± SD estimated terminal half-life of daratumumab associated with linear clearance was 18 ± 9 days when administered as monotherapy and 23 ± 12 days when administered as combination therapy.
For SC daratumumab, Analysis showed a higher max C_{trough} in the 1800 mg cohort in comparison to the max C_{trough} achieved following IV DARA (16 mg/kg) (See figures below)[10]



1.5.1.2.2 Efficacy

Efficacy results for Study MMY2002 and Study GEN501 Part 2 (Part 1 was the dose-escalation phase of this first-in-human study), single-arm, open-label studies in which subjects with relapsed and refractory multiple myeloma were administered 16 mg/kg of daratumumab by intravenous (IV) route as

monotherapy weekly for 8 weeks, every 2 weeks for an additional 16 weeks, and every 4 weeks thereafter until disease progression or unacceptable toxicity. Response and progressive disease assessment in both studies were evaluated based on the International Myeloma Working Group (IMWG) criteria. Efficacy results from the primary analysis of 148 subjects receiving daratumumab 16 mg/kg in Study MMY2002 (n = 106) and Study GEN501 Part 2 (n = 42) were integrated. After a median duration of follow-up of 20.7 months, the median overall survival (OS) was 20.1 months and an overall response rate (ORR) of 31%. Within the individual studies, the ORR was 36% in Study GEN501 and 29% in Study MMY2002.

In Study GEN503, a Phase 1/2, open-label, dose-escalation study of DRd in subjects with relapsed/refractory MM, efficacy results from the primary analysis of 13 subjects (Part 1) and 32 subjects (Part 2) receiving daratumumab 16 mg/kg showed an ORR of 88% and very good partial response of 53% after a median follow up of 7.8 months. Efficacy results from the final analysis showed ORR of 81% and VGPR or better of 69% after median follow-up of 32.5 months. Median PFS has not been established in this study.

In study MMY3003, daratumumab in combination with lenalidomide and dexamethasone (DRd) in relapsed/refractory MM, the primary analysis showed a significant improvement in PFS and ORR for subjects in the DRd group, compared with the lenalidomide/dexamethasone (Rd) group. This represents a 63% reduction in the risk of disease progression or death for the DRd group compared with the Rd group. The ORR for the DRd group was 91% and 75%% for the Rd group.

In Study MMY3004, daratumumab in combination with bortezomib and dexamethasone (DVd) in subjects with relapsed/refractory MM, the primary analysis showed a significant improvement in PFS for subjects in the DVd group, compared with the bortezomib/dexamethasone (Vd) group. This represents a 61% reduction in the risk of disease progression or death for the DVd group compared with the Vd group. The ORR was significant for the DVd group (79%) compared with the Vd group (60%).

For SC daratumumab, the PAVO trials enrolled patients with relapsed and refractory myeloma who had received ≥2 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD). The response rate of SC daratumumab was 52% suggesting efficacy is at least equal or possibly improved compared to IV daratumumab.

1.5.1.2.3 Safety

For IV daratumumab, in the MMY2002 monotherapy trial, the most common treatment emergent adverse events (TEAE) were fatigue (40%), *nausea and anemia (28% each), back pain (26%), cough (24%), neutropenia (23%), pyrexia (22%), upper respiratory* tract infection (22%), and thrombocytopenia (21%). Grade 3 / 4 TEAE were noted in 57% of patients and are *anemia (17%), thrombocytopenia (14%), neutropenia (12%), lymphopenia and pneumonia* (6%), leukopenia and hypertension (5% each), and hypercalcemia (3%).

For IV daratumumab in combination with lenalidomide and dexamethasone (MMY3003 and GEN503), most common TEAE included neutropenia (64%), diarrhea (53%), upper respiratory tract infection (37%), fatigue (37%), anemia (36%), cough (34%), muscle spasms (31%), constipation (31%), thrombocytopenia (29%), viral upper respiratory tract infection (29%), nausea (28%), and pyrexia (25%). Whereas most common Grade 3/4 TEAEs: neutropenia (58%), anemia (16%), and thrombocytopenia (14%).

For IV daratumumab in combination with bortezomib and dexamethasone (MMY3004), the most common TEAEs were thrombocytopenia (60%), peripheral sensory neuropathy (50%), diarrhea (35%), upper respiratory tract infection (33%), anemia (28%), and cough (28%). Grade 3/4 AEs were reported in 81% of subjects; most common were thrombocytopenia (46%), anemia (15%), and neutropenia (14%).

Overall the rate of IRR for IV daratumumab ranges from 40-50% and IRR are mostly noted with the first 1-2 infusions. Most IRR are grades 1 and 2.

For SC daratumumab, Infusion related reactions (IRRs) were reported in 9/41 pts (22%) mostly grade 1/2 in severity including chills, fever, rigors, vomiting, itching, edema of the tongue, non-cardiac chest pain and wheezing. One patient developed grade 3 dyspnea and 1 patient required hospitalization due to fever and chills (both grade 2) after the first infusion. All IRRs developed during or within 6 hours of the first SC infusion and were controlled with antihistamine, corticosteroid, antiemetic, or bronchodilator treatment. No IRRs were reported with subsequent infusions. Overall, the adverse event profile of SC daratumumab was consistent with that of IV use. Grade 3 or higher drug-related adverse events were reported in 5/41 (12%) pts including fatigue (2 pts), influenza, hypertension, dyspnea, and tumor lysis syndrome. SC administration of daratumumab was well tolerated at the abdominal wall injection site with 3/41 (7%) patients reporting grade 1 erythema, induration, or burning sensation.

As of June 29, 2018, approximately 426 patients received SC daratumumab. In order for daratumumab to be absorbed into the body when injected under the skin, it is combined with a substance called rHuPH20 (Hylenex®, recombinant hyaluronidase human injection), also known as co-formulated product. Hylenex® recombinant is used in combination with other medications (in this case, daratumumab) to improve absorption. rHuPH20 has been studied extensively with more than 2321 patients having received it in clinical studies and more than 1,737,832 patients having received the marketed product Hylenex® recombinant.

The most commonly reported adverse events from recombinant human hyaluronidase when injected beneath the skin have been mild injection site reactions, such as redness, pain, bruising, itching, burning, tenderness, swelling, hardness, irritation, tingling, numbness and rash. These reactions were temporary. Moderate injection site reactions have occurred less frequently, including burning, redness, pain, and tingling. Mild to moderate headache has also been reported. Hyaluronidase should not be injected into or around an infected or acutely inflamed area because of the danger of spreading a localized infection. Allergic reactions (urticaria or angioedema) have been reported in less than 0.1% of patients receiving hyaluronidase. Anaphylactic-like reactions following intravenous injections have occurred, rarely.

For further information regarding the safety and efficacy of daratumumab, please refer to the investigator brochure. Daratumumab Hyaluronidase SC (DARZALEX FASPRO) was approved by the FDA for use in multiple myeloma in May 2020 in various combinations including with lenalidomide or with bortezomib.

1.5.2 Lenalidomide

Lenalidomide is approved by the U.S. FDA for the treatment of newly diagnosed multiple myeloma, relapsed and refractory multiple myeloma as well as maintenance therapy for multiple myeloma. Lenalidomide is an immunomodulatory drug that is thought to mediate anti-myeloma activity by 3 main mechanisms: 1) direct antitumor effect; 2) inhibition of the microenvironment support for tumor cells; and 3) an immunomodulatory role.11 Importantly, it has also been shown that lenalidomide causes upregulation of natural killer (NK) cells in myeloma11 and enhances the effector cells of antibody-dependent cell-mediated cytotoxicity, which is one mechanism of action of daratumumab shown in preclinical studies.

Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Lenalidomide can cause significant neutropenia and thrombocytopenia. There is a significantly increased risk of deep vein thrombosis and pulmonary embolism, as well as risk of myocardial infarction and stroke in patients with multiple myeloma who receive lenalidomide with dexamethasone. Higher incidences of secondary primary malignancies were observed in controlled trials of subjects with multiple myeloma receiving lenalidomide. Additionally, administration of lenalidomide has been associated with hepatotoxicity (hepatic failure including fatalities); allergic reactions, including fatalities (hypersensitivity, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis); tumor lysis syndrome including fatalities; and impaired stem cell mobilization (a

decrease in the number of CD34+ cells collected after treatment [>4 cycles]). Most common adverse reactions (≥20%) include diarrhea, fatigue, anemia, constipation, neutropenia, peripheral edema, insomnia, muscle cramp/spasms, back pain, nausea, asthenia, pyrexia, upper respiratory tract infection, cough, rash, dyspnea, dizziness, decreased appetite, thrombocytopenia, and tremor.

1.5.2.1 Daratumumab in combination with lenalidomide and dexamethasone

The combination of daratumumab and lenalidomide dexamethasone resulted in a superior response rate, complete response rate, progression free survival than lenalidomide and dexamethasone in patients with relapsed and refractory myeloma[8]. Importantly the addition of daratumumab to lenalidomide and dexamethasone was associated with a tolerable safety profile: The most common adverse events of grade 3 or 4 during treatment were neutropenia (in 51.9% of the patients in the daratumumab group vs. 37.0% of those in the control group), thrombocytopenia (in 12.7% vs. 13.5%), and anemia (in 12.4% vs. 19.6%)[8]. Daratumumab-associated infusion-related reactions occurred in 47.7% of the patients and were mostly of grade 1 or 2[8].

1.5.3 Bortezomib

Bortezomib is a proteasome inhibitor. It is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in nonclinical tumor models, including multiple myeloma. In addition, bortezomib-based treatment regimens have demonstrated significant improvements in response, progression-free survival (PFS), and OS compared with non-bortezomib-based therapy for multiple myeloma, both in newly diagnosed transplant ineligible patients and those suitable for induction and transplant.Administration of bortezomib has been associated with peripheral neuropathy, hypotension, cardiac toxicity (worsening of and development of cardiac failure), pulmonary toxicity (acute respiratory syndromes), posterior reversible encephalopathy syndrome, gastrointestinal toxicity (nausea, diarrhea, constipation, and vomiting), thrombocytopenia, neutropenia, tumor lysis syndrome, hepatic toxicity, and embryo-fetal risk. Most commonly reported adverse reactions (incidence ≥20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.

1.5.3.1 Daratumumab in combination with bortezomib and dexamethasone

The combination of daratumumab bortezomib and dexamethasone resulted in a higher overall response rate, complete response rate, and progress free survival than bortezomib and dexamethasone in patients with relapsed and refractory myeloma[9]. Importantly, the safety of this combination has been established in the same trial with the most common grade 3 or 4 adverse events reported in the daratumumab group and the control group as follows: thrombocytopenia (45.3% and 32.9%, respectively), anemia (14.4% and 16.0%, respectively), and neutropenia (12.8% and 4.2%, respectively). Infusion-related reactions that were associated with daratumumab treatment were reported in 45.3% of the patients in the daratumumab group; these reactions were mostly grade 1 or 2 (grade 3 in 8.6% of the patients), and in 98.2% of these patients, they occurred during the first infusion.

1.5.4 Dexamethasone

Dexamethasone is a corticosteroid used to decrease the nausea and vomiting associated with chemotherapy as well as for the prevention and treatment of infusion related reactions. Dexamethasone is also an integral part of myeloma therapy and responses to single agent high dose dexamethasone can be noted in nearly half of newly diagnosed patients. In combination with lenalidomide for newly diagnosed myeloma patients, high dose dexamethasone (40 mg PO D1-4, 8-11, 15-19) however results in a higher mortality and morbidity than low dose dexamethasone (40 mg PO D1,8,15,22) which is now the standard

of care. Common adverse reactions include hyperglycemia, increased appetite and weight gain, irritability, insomnia, impaired wound healing, and cataracts and osteoporosis with long-term use.

For further information regarding lenalidomide, bortezomib, and dexamethasone, refer to the individual prescribing information.

1.6 RISK/BENEFIT ASSESSMENT

1.6.1 KNOWN POTENTIAL RISKS

Potential risks of daratumumab
The main risk with IV daratumumab is the potential for infusion related reaction (IRR). The risk of IRR is approximately 40-50% and mostly is noted with the first infusion of daratumumab. Available evidence, although limited in sample size, suggests that SC daratumumab is associated with a lower incidence of IRR (approximately 22%)[10]. Other risks include myelosuppression although it is hard to distinguish this toxicity from the signs of symptomatic myeloma. Additional risks of SC daratumumab include injection site reaction. Additional potential risks are included in the package insert / IB for IV and SC daratumumab respectively

Potential risks for the response adapted approach
The main potential risk of the response adapted approach is a longer time to response given patients will be receiving daratumumab for 2 months prior to the addition of lenalidomide or bortezomib. It is not likely that this potential delay in depth of response would impact the patient negatively but patients who have a more rapid worsening of their myeloma would be taken off study by the treating physician and standard of care therapy would be instituted. It is possible that the duration of benefit from daratumumab monotherapy in responding patient may be shorter than what is expected in patients who receive chemotherapy (lenalidomide or bortezomib). It is unclear however if this would impact the patient's long term outcomes given that salvage therapy in myeloma is effective especially for patients who are lenalidomide or bortezomib naïve. In such light the SWOG 0232 study had randomized newly diagnosed myeloma patients to lenalidomide dexamethasone versus dexamethasone[11]. Patients randomized to dexamethasone had a very short median progression free survival (median 12 months) but did not experience a worse overall survival likely given the ability to cross over and receive active salvage therapy[11].

1.6.2 KNOWN POTENTIAL BENEFITS

Potential benefit of daratumumab
Daratumumab based therapy may be associated with improved outcomes for newly diagnosed myeloma patients who participate in this study. Daratumumab has known direct anti-myeloma effects as well as immunomodulatory effects which result in expansion of cytotoxic T cells and suppression of immunosuppressive cells. In addition, the experience with daratumumab suggests this agent is well tolerated.

Potential benefit for the response adapted approach
Potential participants will be able to receive daratumumab as part of their therapy for newly diagnosed myeloma. Patient will receive SC daratumumab which may be associated with less IRR. Importantly, patients who respond to daratumumab may enjoy a chemotherapy-free treatment on this response adapted approach.

1.6.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

While SC administration of daratumumab is not FDA approved; IV daratumumab, lenalidomide, bortezomib and dexamethasone are all approved by the US FDA for the treatment of newly diagnosed multiple myeloma patients who are not candidate for high dose melphalan and autologous stem cell transplant. Existing data with SC daratumumab suggests a similar efficacy and possibly an enhanced safety and ease of administration over IV daratumumab. SC administration of daratumumab has been FDA approved in May 2020 in various combinations including with lenalidomide or bortezomib combinations).

One aim of this study is to determine the safety and efficacy of daratumumab (a chemotherapy free therapy) for patients with newly diagnosed multiple myeloma. However to minimize the risk of under treatment and in light of the fact that salvage therapy is effective, we have used a response adapted treatment design. As such, patients who don't achieve a partial response to daratumumab in the first 2 cycles (months) of therapy, will receive the addition of lenalidomide or bortezomib which represent standard of care as they are approved second line regimens. The decision to add bortezomib or lenalidomide will be at the discretion of the treating physician based on which agent is anticipated to have a better tolerance, the patient choice but also informed by ex vivo testing (EMMA). If such therapy is shown to be safe and effective, it could prove to be a chemotherapy free regimen for patients with newly diagnosed myeloma and hence spare toxicity from patients (especially for older adults who are particularly at risk for such complications).

2 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the efficacy of a daratumumab based response adapted approach	To determine the best response (Overall response rate: rate of partial response and better) to therapy per the uniform response criteria of the IMWG as assessed by the study investigators	The overall response rate (ORR) assessment is a commonly used endpoint in newly diagnosed myeloma trials. This is because it can be assessed more rapidly than PFS and OS
Secondary		
To evaluate the safety profile of daratumumab based therapy in older adults with newly diagnosed myeloma To identify potential biomarkers for the prediction of response to therapy in MM	To determine the 1 and 2 years progression free survival (PFS) of the study population To determine the overall response rate (ORR) (partial response or better) after 2 cycles of daratumumab To determine the 2 year overall survival of this response adapted approach The proportion of patients who remains on daratumumab monotherapy To evaluate the safety of this therapy using the NCI CTC version 5.0 with a particular	While ORR is the primary endpoint, PFS and OS will be evaluated as well. The study will also allow the evaluation of the response to 2 cycles of daratumumab monotherapy. . Safety evaluation is a necessary component of MM studies given the non curative nature of therapy. We will evaluate a possible biomarker of

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	attention to the rate of IRR with SC daratumumab To determine agreement between actual responses and responses as predicted by an Ex Vivo Mathematical Myeloma Advisor (EMMA)	response (namely an ex vivo drug sensitivity testing termed EMMA)
Tertiary/Exploratory		
To study changes in immune profiling with daratumumab therapy To attempt to validate EMMA in silico prediction and dynamics of response To evaluate a frailty index as a tool for older adults with myeloma treated with novel agents	Explore changes in immune profiling at baseline and after daratumumab dexamethasone Validate EMMA in silico predictions of daratumumab response. Incorporate clinical parameters and early dynamics of monoclonal paraprotein response to therapy to extend EMMA's capacity to include longer term predictions of patient outcomes. Correlate a simplified geriatric assessment (frailty) and grade 3 and 4 (hematologic and non-hematologic) toxicity from therapy as well as discontinuation due to adverse events To determine the proportion of patients who are without minimal residual disease (MRD-) using Next Generation sequencing (NGS)	Given daratumumab's mechanism of action, immune profiling is an attractive tool to investigate. Geriatric assessments have not been validated with daratumumab based monotherapy for newly diagnosed myeloma patients MRD assessment are an important tool for newly diagnosed myeloma studies to better assess the depth of response. This will be done for patients who achieve VGPR or better. However it is unknown how many patients may require MRD testing with this approach and this is an exploratory aim

3 STUDY DESIGN

3.1 OVERALL DESIGN

This is a single site, open label phase II response adapted clinical trial. In this response adapted approach, older adults with newly diagnosed symptomatic multiple myeloma will receive daratumumab and dexamethasone for 2 months. Patients who achieve a partial response or better will continue on daratumumab. Patients who achieve less than a partial response will have lenalidomide or bortezomib added to their therapy. Patients who experience progressive disease on daratumumab after the initial 2 months of monotherapy or on the combination of daratumumab and either lenalidomide or bortezomib will

come off study. Because of the design, 3 arms may be defined (Arm A: daratumumab dexamethasone, Arm B: daratumumab lenalidomide and dexamethasone, and Arm C: daratumumab bortezomib and dexamethasone).

3.2 END OF STUDY DEFINITION

In general, patients will continue on study until progressive disease or unacceptable toxicity. Specifically, patients will continue to receive therapy on study until one of the following has been met:

1- Progressive disease
2- Unacceptable toxicity which in the assessment of the investigator alters the risk / benefit assessment for the patients
3- A change in the medical condition of the patient which alters the risk / benefit assessment for the patient
4- Noncompliance and nonadherence of the patient with the study assessments that could result impact patient safety
5- Patient preference

Patients who discontinue study therapy will be followed for reasons other than progressive disease will be followed every 3 months or until another therapy is initiated to assess for progression. This can be done by telephone and review of records.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Understand and voluntarily sign an informed consent form.

2. Age ≥ 65 years and presence of coexisting conditions which in the opinion of the treating physician are likely to result in the development of unacceptable side effects associated with high-dose chemotherapy with stem-cell transplantation

3. Able to adhere to the study visit schedule and other protocol requirements.

4. Diagnosed with multiple myeloma and be considered to have active disease with either CRAB criteria (hypercalcemia, renal failure, anemia, or bone lesions) or myeloma defining events (bone marrow ≥ 60% plasma cells, sFLC ratio≥ 100 or MRI or PET defined lesions) (Appendix C). Patients must not have received an active chemotherapy regimen. Patients may have received palliative radiotherapy at least 2 weeks prior to the study start. Dexamethasone up to 160 mg total dose is allowed prior to participation

5. Measurable myeloma paraprotein levels in serum (≥ 0.5 g/dL), urine (≥ 0.2 g excreted in a 24-hour urine collection sample) or by serum free light chains (involved free light chain greater than 100mg/L)

6. Eastern Cooperative Group (ECOG) Performance Status of 0 - 2.

7. Serum bilirubin levels ≤1.5 times the upper limit of the normal range for the laboratory (ULN).

8. Serum AST or serum ALT] levels ≤2 x ULN

9. Must have adequate bone marrow function:

    a. Absolute neutrophil count $\geq$ 1,000 cells/mm^3 (1.0 x 10^9/L).

    b. Platelets $\geq$ 75,000 /mm^3.

10. Hemoglobin > 8 g/dL (transfusions are allowed)

11. Calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula.

12. Men must agree to use a latex condom during sexual contact with a female of child bearing potential even if they have had a successful vasectomy. See Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

4.2 EXCLUSION CRITERIA

The presence of any of the following will exclude a subject from study enrollment:

1. Ongoing severe infection requiring intravenous antibiotic treatment.

2. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in-situ cervical cancer, or other cancer from which the subject has been disease-free for at least 2 years.

3. Solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia.

4. Patients with known COPD with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal and , moderate or severe persistent asthma within the past 2 years or uncontrolled asthma. Patients with a history of COPD will have pulmonary function testing to include FEV1

5. Uncontrolled medical problems such as diabetes mellitus, congestive heart failure, coronary artery disease, hypertension, unstable angina, arrhythmias), pulmonary, hepatic and renal diseases unless renal insufficiency is felt to be secondary to multiple myeloma.

6. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

7. Pregnant or lactating females.

8. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

9. Concurrent use of other anti-cancer agents or treatments with the exception for hormonal therapy which is allowed.

10. Known allergy or hypersensititvity or intolerance to any of the study drugs, hyaluronidase, mAbs, human proteins, or their excipients (refer to daratumumab IB), or known sensitivity to mammalian-derived products

11. Seropositive for human immunodeficiency virus (HIV)

12. 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.

13. 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).

4.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a modifiable factor may be rescreened (for example laboratory assessment). Rescreened participants should be assigned the same participant number as for the initial screening.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be identified by a myeloma physician in the outpatient clinic of the departments of Malignant Hematology or Blood and Marrow and Cellular Immunotherapy at H. Lee Moffitt Cancer Center and Research Institute. We anticipate the median age of patients enrolled to be approximately 75 years and about half the patients to be male based on a prior study for this patient population conducted at our center.

5 STUDY INTERVENTION

5.1 DARATUMUMAB

5.1.1 DARATUMUMAB

Daratumumab is approved by the U.S. FDA for the treatment of newly diagnosed as well as relapsed myeloma. Importantly it is approved as monotherapy as well as in combination with lenalidomide, or bortezomib or pomalidomide. SC daratumumab (DARZALEX FASPRO) was FDA approved for use in various combination for multiple myeloma patients in May 2020. The study will transition to commercial DARZALEX FASPRO supplied by Janssen for this study.

5.1.2 DARATUMUMAB DOSING AND ADMINISTRATION

Patient will receive daratumumab (1800 mg in 15 ml) premixed with recombinant human hyaluronidase enzyme (rHuPH20 30,000 units) to be administered by manual subcutaneous injections over 3-5 minutes on the following schedule: weekly for the first 8 weeks, every other week for the next 16 weeks and every

4 weeks after. Injections will be using a 23G or 25G (5/8 inch or 1 inch) needle in the subcutaneous tissue in the abdomen. Injections sites will be rotated between individual doses.

No dose reduction for daratumumab will be planned. **Only if any of the following criteria are met and the event cannot be ascribed to lenalidomide, bortezomib, dexamethasone, or underlying multiple myeloma, the daratumumab injection must be held to allow for recovery from toxicity.** The criteria for a dose delay are:

- Grade 4 hematologic toxicity (except for Grade 4 lymphopenia), or Grade 3 or higher
- Thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Grade 4 Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
    - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment
    - Grade 3 diarrhea that responds to antidiarrheal treatment
    - Grade 3 fatigue or asthenia that was present at baseline and lasts for <7 days after the last administration of daratumumab
    - Grade 3 or 4 electrolyte disturbances which can be managed with replacement therapy

If daratumumab administration does not commence within the prespecified window of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date

The following premedication will be administered prior to daratumumab:

Acetaminophen 650-1,000 mg PO once

Cetirizine 10 mg PO once, or equivalent dose of another antihistamine, either PO or IV

Dexamethasone 20 mg PO once (unless dose reduced)

Montelukast 10 mg PO once. Montelukast may be omitted for any daratumumab dose after the second injection if the subject has no respiratory symptoms.

All patients treated with SC daratumumab should be observed for at least 6 hours after the end of the SC injection on C1D1 and if deemed necessary by the investigator / treating physician, after subsequent injections. Vital signs (Heart rate, blood pressure, respiratory rate, temperature) should be monitored before, at the end of the SC injection, 30 and 60 min after the SC injection for the first injection only. For all other administrations, vital signs should be measured before the start of injection and at the end of the injection. If the subject experiences any significant medical event, then the investigator should assess whether the subject should stay overnight for observation.

5.1.2.1 MANAGEMENT OF INFUSION-RELATED REACTIONS

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

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids as needed. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, and/or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied. Cases of severe reaction should be discussed with the Principal Investigator / Sponsor
- For IRR adverse events (other than laryngeal edema or bronchospasm) that are Grade 3, the daratumumab administration must be stopped and the participant must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the daratumumab administration may be restarted at the investigator's discretion. If the intensity of the adverse event returns to Grade 3 after restart of the daratumumab administration, then the participant must be withdrawn / permanently discontinued from daratumumab treatment.

5.1.3 DARATUMUMAB HANDLING / STORAGE AND ACCOUNTABILITY

5.1.3.1 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The final daratumumab SC product for oncology/hematology is daratumumab at a target concentration of 120 mg/mL co-formulated with rHuPH20 in a 25R vial at a nominal fill of 15 mL.

5.1.3.2 PRODUCT STORAGE AND STABILITY

The daratumumab SC vials should be stored in the original carton in a refrigerator at 2ºC to 8ºC and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Any unused portion remaining in a daratumumab IV or SC vial must be discarded since daratumumab IV or SC does not contain preservatives.

5.2 DEXAMETHASONE

5.2.1 DEXAMETHASONE

Commercial dexamethasone will be used in this study

5.2.2 DEXAMETHASONE DOSING AND ADMINISTRATION

The dexamethasone starting dose will be 20 mg PO once a week. Commercial dexamethasone will be used. Dexamethasone is often supplied in 4 mg tablets. Accordingly, patients will take 5 (4 mg tablets) one day of the week prior to the administration of daratumumab if this corresponds to a daratumumab dosing days. In non daratumumab dosing days, dexamethasone will be taken by the patient at home, usually in the morning with breakfast.

5.2.3 DEXAMETHASONE PREPARATION / HANDLING / STORAGE AND ACCOUNTABILITY

Commercial dexamethasone will be used and will be handled and stored per package insert.

5.2.4 DEXAMETHASONE DOSE REDUCTION

The following dose reduction schedule for dexamethasone will be used

DL1: Dexamethasone 20 mg PO D1,8,15,22 of a 28 days cycle

DL-1: Dexamethasone 10 mg PO D1,8,15,22 of a 28 days cycle

DL-2: Dexamethasone 4 mg PO D1,8,15,22 of a 28 days cycle

DL-3: Discontinue dexamethasone

The following table will be used for dexamethasone dose modification although the treating physician has the discretion to reduce dexamethasone dose for a lower grade AE if clinically indicated.

CTCAE CATEGORY ADVERSE EVENT	**ADVERSE EVENT**	**TREATMENT ADJUSTMENT**
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2	It is recommended patient receive proton pump inhibitors (PPI), such as omeprazole as prevention. However if the patients is not on PPI, start PPI. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
	> Grade 3	Hold corticosteroids until symptoms are adequately controlled. Reduce by 2 dose levels along with concurrent therapy with PPI or other. If symptoms persist despite above measures, discontinue corticosteroids and do not resume.
	Acute pancreatitis	Discontinue corticosteroids and do not resume
Cardiovascular	Edema > Grade 2	Diuretics as needed, and decrease corticosteroids dose by 1 dose level; if edema persists despite above measures decrease dose by 2 dose levels from the initial dose; discontinue corticosteroids and do not resume if symptoms persist despite reduction.
Neurology	Confusion or Mood alteration > Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold corticosteroids until symptoms resolve to $\leq$ grade1. Reduce dose by 2 dose levels from current dose. If symptoms persist despite above measures, discontinue corticosteroids and do not resume.

Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease corticosteroids dose by 1 dose level; If weakness persists despite above measures decrease dose by 2 dose levels from the initial dose. Discontinue corticosteroids and do not resume if symptoms persist despite reduction.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by 1 dose level decrements until levels are satisfactory

5.3 LENALIDOMIDE

5.3.1 LENALIDOMIDE

Commercial supply of lenalidomide will be used.

5.3.2 LENALIDOMIDE DOSING AND ADMINISTRATION

Lenalidomide will be given orally on days 1-21 of a 28 days cycle. The starting dose of lenalidomide will be based on the patient creatinine clearance and age.

The starting dose of lenalidomide will be 10 mg if the creatinine clearance is < 50 ml/min or the patient is over 80 years of age, 15 mg if the patient is 75 years of age or older and the creatinine clearance is >50 ml/min; and 25 mg if the patient is <75 years and with a creatinine clearance of 50 ml/min. Patients with a creatinine clearance < 30 ml/min are not eligible but patients who experience a deterioration in the renal function during screening or treatment may continue on lenalidomide therapy as long as the risk / benefit profile is deemed acceptable, that study therapy is in the best interest of the patient and after discussion with the study principal investigator / sponsor.

Given lenalidomide supply is commercial, it is possible that at times, the lenalidomide monthly supply is not available on the first day of a cyle. If lenalidomide is not anticipated to be available for at least 7 days after D1 of the cycle, the dosing of all study drugs (dexamethasone / daratumumab) will be delayed until lenalidomide is available again in an attempt to stay on schedule with all study drugs. On the other hand, if lenalidomide delays are anticipated to be less than 7 days, it is ok to proceed with daratumumab and dexamethasone and lenalidomide would be started when it is obtained but missed doses will not be replaced and patients will stop lenalidomide on D21 of the cycle.

If a patient skips or forgets a lenalidomide dose, the dose will not be made up.

5.3.3 LENALIDOMIDE PREPARATION / HANDLING / STORAGE AND ACCOUNTABILITY

Commercial Lenalidomide will be used for this study. It will be stored, handled per the package insert requirement. In addition, a dosing diary will be provided to patients for drug accountability.

5.3.4 LENALIDOMIDE DOSE REDUCTION

The following dose levels of Lenalidomide will be used:

Dose level 1: 25 mg PO D1-21 of a 28 days cycle

Dose level -1: 15 mg PO D1-21 of a 28 days cycle

Dose level -2: 10 mg PO D1-21 of a 28 days cycle

Dose level -3: 5 mg PO D1-21 of a 28 days cycle

Dose level -4: 2.5 mg PO D1-21 of a 28 days cycle

Dose level -5: discontinue lenalidomide

The table below will review guidelines for lenalidomide dose reduction although the treating physician has the discretion to reduce the lenalidomide dose for a lower grade AE if clinically indicated.

CTCAE CATEGORY ADVERSE EVENT	**CTCAE GRADE**	**TREATMENT ADJUSTMENT** **Maintenance Phase**
Neutropenia	Grade 3 with fever or Grade 4	Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle at the dose detailed below. Alternatively if the toxicity occurred during the first 2 weeks of the cycle, then hold lenalidomide until the toxicity improves to ≤ grade 2 and resume lenalidomide as detailed below. First occurrence: when resolved to ≤ grade 2 begin next cycle with one dose level reduction of lenalidomide Second occurrence: when resolved to ≤ grade 2 begin next cycle with one level dose reduction of lenalidomide Subsequent dose reductions of lenalidomide are permitted at the investigators discretion.
Thrombocytopenia	Grade 4	Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle with one dose level reduction in lenalidomide. Alternatively if the toxicity occurred during the first 2 weeks of the cycle, then hold lenalidomide until the toxicity improves to ≤ grade 2 and resume lenalidomide with one dose level reduction.
Cardiac toxicity	Arrhythmia ≥ grade 2	Hold lenalidomide until resolved to ≤ grade 1. Resume at one dose level reduction of lenalidomide.
	Arrhythmia ≥ grade 3	Discontinue lenalidomide at the investigators discretion.

	Congestive heart failure ≥ grade 2	Discontinue lenalidomide at the investigators discretion.
Hyperthyroidism/ Hypothyroidism	Any grade	Hold lenalidomide and evaluate patient for other causes. May resume therapy at the same dose once patient is stable at investigators discretion.
Non desquamating rash	Grade 2	Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle with one dose level reduction in lenalidomide if the toxicity resolves to less than grade 2. Alternatively if the toxicity occurred during the first 2 weeks of the cycle, then hold lenalidomide until the toxicity improves to < grade 2 and resume lenalidomide with one dose level reduction.
	Grade 3 or 4	Discontinue protocol therapy.
Desquamating rash or Erythema Multiforme	Any grade	Discontinue protocol therapy.
Allergic reaction or hypersensitivity	Grade 2 or 3	Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle with one dose level reduction in lenalidomide if the toxicity improves to less than grade 2. Alternatively if the toxicity occurred during the first 2 weeks of the cycle, then hold lenalidomide until the toxicity improves to less than grade 2 and resume lenalidomide with one dose level reduction.
	Grade 4	Discontinue lenalidomide
Venous thrombosis/embolism	≥ Grade 3	Hold (interrupt) dose, therapeutic anticoagulation as appropriate; restart at investigator's discretion (maintain dose level)
Other non-hematologic toxicity except those events specifically attributed to dexamethasone as outlined in table 4.	Grade 3 / 4	Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle with one dose level reduction in lenalidomide. Alternatively if the toxicity occurred during the first 2 weeks of the cycle, then hold lenalidomide until the toxicity improves to ≤ grade 2 and resume lenalidomide with one dose level reduction.

5.4 BORTEZOMIB

5.4.1 BORTEZOMIB

Commercial supply of bortezomib will be used in this study

5.4.2 BORTEZOMIB DOSING AND ADMINISTRATION

Bortezomib will be given weekly subcutaneously in an effort to decrease the toxicity of the therapy. Specifically patients will receive a starting dose of bortezomib of 1.3 mg/m2 SC D1,8,15 of a 28 day cycle. Bortezomib will be administered per standard of care procedures. After 8 cycles of bortezomib based therapy (cycle 10 of the trial), patients may receive a less frequent maintenance dose of bortezomib (dose reduction to bortezomib on days 1 and 15 every 28 days or discontinue bortezomib but continue on daratumumab) at the discretion of the treating physician.

5.4.3 BORTEZOMIB PREPARATION / HANDLING / STORAGE AND ACCOUNTABILITY

Bortezomib will prepare, handled and stored per standard of care procedures outlined in the package insert.

5.4.4 BORTEZOMIB DOSE REDUCTION

The following dose levels of bortezomib will be considered in this study:

Dose level 1: bortezomib 1.3 mg/m2 SC D1,8,15 of a 28 days cycle

Dose level -1: 1mg/m2 SC D1,8,15 of a 28 days cycle

Dose level -2: 0.7 mg/m2 SC D1,18,15 of a 28 days cycle

Dose level -3: discontinue bortezomib

Guidelines for bortezomib dose reduction are shown below:

Dose adjustments should be based on the highest grade of toxicity that is ascribed to bortezomib. Bortezomib therapy should be withheld at the onset of any Grade 3 or Grade 4 non-hematological or Grade 4 hematological toxicities excluding neuropathy. In addition, the treating physician has the discretion to reduce bortezomib dose for a lower grade AE if clinically indicated. Once the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at a reduced dose level.

The following table outlines bortezomib dose reductions for neuropathy:

CTCAE CATEGORY ADVERSE EVENT	**CTCAE GRADE**	**TREATMENT ADJUSTMENT**
Neuropathy	Grade 1 (asymptomatic, loss of deep tendon reflexes or paresthesias) without pain or loss of function	No action
	Grade 1 with pain or	Reduce bortezomib by 1 dose level

	Grade 2 (moderate symptoms, limiting instrumental ADL)	
	Grade 2 with pain or Grade 3 or 4 (severe symptoms, limiting self-care ADL)	Discontinue bortezomib

Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc.

Self-care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

5.5 STUDY INTERVENTION COMPLIANCE

Daratumumab will be administered in the cancer center and compliance will be easily monitored with review of the electronic health record. It is anticipated that SC daratumumab would be associated with better compliance than IV daratumumab given quicker infusion times and possibly a lower rate of IRR.
Bortezomib will be administered in the cancer center and compliance will be monitored with review of the electronic health record.
Dexamethasone and lenalidomide are orally given on non treatment days and a diary will be provided for patients.

5.6 CONCOMITANT THERAPY

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Patients will receive concomitant medications to treat symptoms, adverse events and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc. are allowed.

1. Use of blood products and growth factors

Patients may receive red blood cell (RBC) or platelet transfusions, if clinically indicated, per institutional guidelines. Appropriate anti-coagulation is allowed during the study (eg: LMW heparin, direct factor Xa inhibitors, etc). Patients may receive supportive care with erythropoietin, darbepoetin, G-CSF or GM-CSF in accordance with clinical practice or institutional guidelines prior to entry and throughout the study.

2. Glucocorticoid therapy

Patients must receive corticosteroid therapy as part of the treatment regimen. Additional corticosteroid are allowed for the treatment of non-malignant conditions (inflammatory disorders or adrenal insufficiency) provided the dose does not exceed the equivalent of 20 mg of prednisone daily

3. Radiation Treatment

The need for radiation therapy is generally considered to be a treatment failure. However, an exception (that is patients allowed to remain in the treatment phase of the study) is made for radiation therapy to a pathological fracture site to enhance bone healing or to treat post-fracture pain that is refractory to narcotic analgesics because pathologic bone fractures do not by themselves fulfill a criterion for disease progression

4. Proton pump inhibitors

The use of proton pump inhibitors (for example omeprazole) will be recommended for the prevention of dexamethasone toxicity as is clinical practice

5. Bisphosphonate

The use of bisphosphonates or denosumab for the prevention of skeletal related events due to myeloma is allowed per routine clinical care.

6. IVIG

The use of intravenous immunoglobulins for the prevention of recurrent infections in patients with hypogammaglobulinemia is allowed per routine clinical practice

7. Antiviral prophylaxis

Prophylaxis for varicella zoster reactivation will be required for all patients. Examples of appropriate prophylaxis is acyclovir. 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.

8. Venous thromboembolic event prophylaxis

Prophylaxis for venous thromboembolic events will be required for all patients receiving lenalidomide. The prophylactic strategy will be at the discretion of the treating physician. In general, aspirin 81 mg PO daily is recommended for patients at low risk for thromboembolic event whereas low molecular weight heparin or other anticoagulants are recommended for patients at high risk for venous thromboembolic events.

Prohibited Medications

Concurrent therapy with an approved or investigative anticancer therapeutic, other than glucocorticoids and therapy defined per the protocol is not allowed.

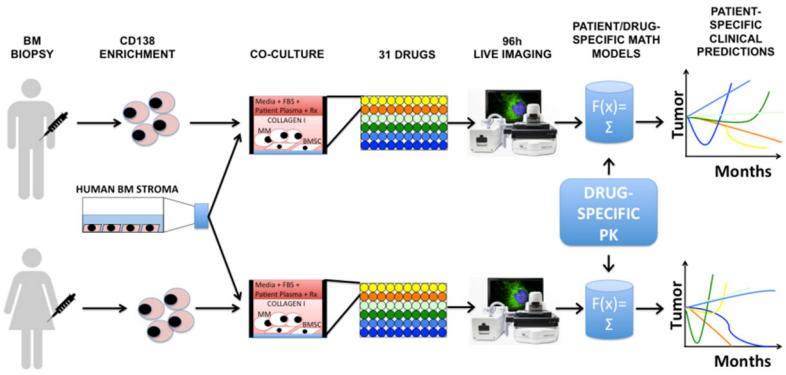
Use of any immunosuppressive agents during the study is not allowed

Other investigational agents should not be used during the study.

6 CORRELATIVE STUDIES

6.1 EMMA

Within the context of this trial, we aim to pursue a personalized treatment schema that best allocates the use of either Bortezomib or Lenalidomide in patients who do not achieve at least a partial response to subcutaneous datatumumab and dex after 8 weekly doses. Carry this out, we have developed a platform, EMMA (***e****x vivo* ***m****athematical* ***m****alignancy* ***a****dvisor*), consisting of patient-specific mathematical models parameterized by an *ex vivo* assay that reverse engineers the intensity and heterogeneity of sensitivity of primary cells from patients to up to 31 drugs simultaneously. This unique *in silico* platform predicts months of therapeutic response in patients within a clinically actionable time frame (5 days) using fresh tissue, *ex vivo* response/resistance data, mathematical models and drug-specific pharmacokinetics, with a high predictive accuracy, to multiple classes of drugs(**Figure**)[12, 13]. EMMA's accuracy, reproducibility, short turnaround time and high-throughput potential demonstrate promise as ***(i)*** a patient specific decision-support system for therapeutic management, ***(ii)*** *in silico* clinical trials, wherein a single cohort of patients is simultaneously tested against multiple drugs and regimens and ***(iii)*** when paired with high fidelity molecular sequencing, a predictive biomarker discovery tool. Collectively, EMMA has great potential to augment clinical decision making for oncologists and our patients. Within this clinical trial, we focus on advancing this novel predictive *in silico* modeling approach to accelerate utilization of clinical decision support tools for the delivery of personalized therapies. Further, EMMA's capabilities also extend to agents in early clinical and preclinical development highlighting the potential for improved clinical trial matching and accelerated drug discovery



We respectfully submit that our *ex vivo* system is highly innovative platform for personalized therapy. *First*, EMMA is a phenomenological mathematical model based on *ex vivo* drug response, measured

directly in patient-derived MM cells, to predict longer-term response to therapy. This unique methodology for personalized oncology does not make the assumption that targeting a specific pathway (or gene) using genetic profiling of the bulk tumor will result in durable responses. Instead, we use empirical data (1,920 data points per drug) from a patient's cancer cells to obtain information on drug sensitivity/resistance. This is essential in view of findings that as of today genomic mutations are a poor indicator of drug efficacy, even in targeted therapy. As such, phenomenological models based on methods to monitor individual cells have the potential to be more reliable because they are based on actual measurements from the data, as opposed to network-diagram based models, which are based on intuition or literature, and are then "molded" into the data. *Second*, unlike similar efforts that cultivate patient cells and test drugs using cell death as readout, we use validated mathematical models to predict how drugs will perform clinically based on *ex vivo* cell death kinetics, accounting for *in vivo* pharmacokinetics (PK), tumor heterogeneity and TME. Thus, EMMA accounts for critical components of tumor drug sensitivity/resistance not previously accounted in *ex vivo* modeling. *Third*, EMMA's characteristics represent significant advantages over historical colony formation assays (CFA) and contemporary patient derived xenograft (PDX) drug sensitivity models in terms of clinical translation. *Forth*, EMMA is high throughput. It can be used for personalized testing of up to 127 drugs or drug combinations simultaneously (including immunobiologics) on as few as 1 million patient cells. To this end, each patient is "enrolled" on up to 127 *in silico* clinical trials simultaneously. Recall, this means that each patient samples tested on this trial will also be test 127 drugs/regimens simultaneously. ***Fifth,*** EMMA is scalable. We recognize that additional aspects of MM tumor biology, patient biology and the TME (immune and supportive) contribute to drug response and the evolution of drug resistance. Critically, we will test the incorporation additional representative data elements in predictive accuracy within the exploratory aims of this trial. ***Sixth,*** EMMA samples are uniquely paired with both whole exome sequencing (WES) and RNA sequencing (RNAseq). Thus, we have an *ex vivo* high throughput platform for investigation of molecular profiles and mechanisms of response to single agents and combinations to improve predictive modeling of EMMA, discover tumor vulnerabilities and identify critical molecular signatures of response for molecular-based trial matching. ***Finally*****,** we anticipate that EMMA affords a radical change in the allocation of therapeutic regimens to patients, moving beyond current "one-size-fits-all" management system, where a regimen is assigned to a group of patients according to shared observable characteristics, irrespective of inter-patient and intra-tumoral heterogeneity. EMMA is a platform to assist clinicians in assigning the right patient the right drugs at the right time.

Preliminary Data and Current State of Technology: With EMMA we propose a radical change in the way therapeutic regimens are assigned to patients, moving away from a "boxing" classification system wherein the same regimen is assigned to a group of patients according to inclusion criteria based on shared observable characteristics (genetic, epigenetic, clinical history) irrespective of unobservable traits (inter-patient and intra-tumoral heterogeneity). To provide a more personalized approach for the allocation of therapy, we have developed a system consisting of patient-specific mathematical models parameterized by an *ex vivo* assay that reverse engineers the intensity and heterogeneity of drug sensitivity of primary cells from MM patients to up to 31 drugs simultaneously. This unique *in silico* platform was specifically designed to translate 4 days of *ex vivo* response/resistance data, mathematical models, and drug-specific PK data, into months of clinical response . Our recent data demonstrates that EMMA has high predictive accuracy with patients treated with multiple classes of drugs, in addition to high reproducibility, short turnaround time and high-throughput potential.

EMMA represents a platform for truly personalized therapy by proactively estimating clinical benefit and providing a means to minimize use of ineffective agents with potential avoidable toxicity and financial burden. This transformative potential stems from the nature of EMMA's end product: trajectories of predicted clinical response validated in real time by surrogates of clinical response (paraprotein in MM, lymphadenopathy, malignant cells in peripheral blood in MCL and other HEME). As such, EMMA stands out from current prognostic biomarkers and companion biomarkers. Current prognostic tools only indicate risk of shorter survival, but do not suggest a preferred therapy. Similarly, companion biomarkers are tailored to a particular drug or regimen and are more often a tool to discard the use of therapies rather than to actually dictate treatment. Lastly, EMMA can predict clinical outcomes for off-label drugs and used

to estimate clinical response to drug combinations or schedules for which they have not been trained. To this end, we anticipate that EMMA represents a "*novel predictive* ex vivo *and/or* in silico *modeling approach to accelerate preclinical research and development of personalized therapies*."

Accuracy and reproducibility of EMMA's clinical predictions: From a cohort of 52 MM patients, EMMA correctly classified 96% as responders/non-responders and correctly classified 79% according to IMWG stratification of level of response. The strictest validation of this model is the direct correlation of the tumor burden predictions with all available tumor burden measurements. The regression line between *in silico* model predictions and clinical response, shown flanked by the 95% confidence interval, had a slope of 0.83 and Pearson correlation coefficient r=0.5658 (P<0.0001). Furthermore, we have demonstrated excellent concordance in inter-day, inter-laboratory and intra-plate reproducibility. It is also important to note that most of the dispersion observed stems from non-responders, whose clinical outcome is not driven by chemosensitivity but rather by tumor growth rate.

Wide range of agents: EMMA is able to assess up to 31 drugs simultaneously. We have published successful and accurate results of EMMA on all therapeutics evaluated, including proteasome inhibitors, immunomodulatory drugs (IMIDs), steroids, DNA damaging agents, acetylase inhibitors, nuclear export inhibitors, protein kinase inhibitors (PKI) among others. We have also demonstrated activity of monoclonal antibodies (critically, daratumumab) recapitulating both drug-induced and immune-mediated cell death. This is, in part, due to the organotypic nature of EMMA, where each well is a re-construction of the bone marrow microenvironment, including patient-derived soluble factors and bone marrow stroma. While the simultaneous testing of 31 drugs in a patient encompasses a relatively wide range of agents, we are currently expanding this capability to 127 drugs in 1,536 well plates to capture a larger number of relevant compounds and combinations.

Exploratory Objectives.

Validate EMMA's ability to predicted response to daratumuamb and characterize patient specific immune TME. Consistent with known mechanism of action, antibody dependent cellular phagocytosis (ADCP), our preliminary studies with daratumumab (Dara) has shown MM-specific cell death due to ADCP after at least 3-4 days of exposure to daratumumab**.** EMMA's preliminary clinical predictions of 11 MM patients to single agent daratumumab agree with patient status (no response in 3 Dara-refractory patients and estimated response in 4 of 8 Dara-naïve patients). Although very promising, we need to confirm that this sensitivity readout translates to accurate predictions of clinical response. *Technical Validation:* The same accuracy metrics will be applied as previously published[14] will be applied to the patients enrolled in this clinical trial. Should this direct method of prediction fail (<96% accuracy responders/no-responders[14]), we will determine if the order of sensitivity determined by *ex vivo* LD50 or AUC correlates with actual clinical sensitivity, suggesting a means to estimate clinical efficacy of mAbs by comparison to previously tested patients). *Additional/alternative plans.* Additional relevant questions also being addressed: (a) cell of origin of the phagocytes, (b) dependency of *ex vivo* responses on density of these MM phagocytic cells, (c) physiological cell density and malignant-to-phagocyte ratio, and (d) EMMA's current PK model adequacy for this drug-to immune cell-MM cell interaction accounting for indirect activities of these immunologic agents.

Incorporate clinical parameters and early dynamics of monoclonal paraprotein response to therapy to extend EMMA's capacity to include longer term predictions of patient outcome. While response predictions have the potential for immediate impact on patient care, response rates represent an indirect measure of clinical success in MM, thus here we incorporate additional parameters to extend EMMA's predictive capabilities to time to progression (TTP).

6.2 IMMUNE PROFILING

The immune Tumor MicroEnvironment (TME) is defined by both cellular and soluble extracellular elements, necessitating a multi-modality approach to achieve a comprehensive characterization of these components.

Gene expression profiling (GEP) affords a powerful global assessment and the nCounter™ PanCancer Immune Profiling Panel (NanoString Technologies) provides a robust platform for simultaneous assessment of 770 immune-related genes. Purified mRNA isolated from marrow aspirate samples will be processed for GEP in the Moffitt Molecular Genomics Core Facility according to protocol specifications. Raw data will be analyzed using the nSolver™ proprietary software (NanoString) and with the assistance from the Moffitt Cancer Informatics Core. Multiparameter flow cytometry, utilizing 4 comprehensive, high-parameter panels detailed in Table 2, offers high resolution detail at the single-cell level.

The myeloid panel incorporates a broad assortment of cell surface markers to allow for in-depth characterization of the myeloid populations including dendritic cells, macrophage, neutrophils, and myeloid-derived suppressor cells. Three lymphoid panels are designed to resolve T cell and NK cell populations, with extensive classification of T cells in particular, measuring maturation state (naïve, central memory, effector memory, effector and memory stem cells), subset composition (eg. T_H1, T_H2, T_H17, T_{REG}, and $CD8^+$ counterpart populations, and activation/exhaustion status (eg. PD-1, CTLA-4, TIM-3, Lag3, BTLA, CD27, 2B4 expression). Once prepared for analysis, data acquisition will be performed on a FACSymphony cytometer housed and maintained in the Moffitt Flow Cytometry Core Facility. Data analysis will be performed on FlowJo software using both classic phenotype-defined and computer-based non-supervised principal component approaches which will be merged to provide additional analytic insight. Soluble factor concentrations in the extracellular marrow environment will be analyzed by bead-capture-based assay using the Lunaris™ system (Ayoxxa Biosystems) offering an efficient multiplex strategy for cytokine and chemokine quantification (Table 3). APRIL (A PRoliferation-Inducing Ligand) and BAFF (B cell Activation Factor) concentrations will continue to be assessed via ELISA assay (Invitrogen), analyzed on a Cytation[3] Imaging Reader (BioTek). Collectively, these measures of immune populations and the cytokine communication networks will provide informative insights into the dynamic immunologic interactions in the TME. Comprehensive gene expression profiling will provide population-level perspective while unifying the more granular details provided by the high-resolution analysis of cellular and soluble factor elements.

Table 2. Multiparameter Flow Cytometry Panel Descriptions

Panel Name	Cellular Markers Assessed
Myeloid Panel	CD3, CD11b, CD11c, CD14, CD15, CD16, CD19, CD32, CD33, CD34, CD36, CD41a, CD45, CD64, CD71, CD163, HLA-DR, Live/Dead Aqua
Lymphoid Maturation Panel	CD3, CD4, CD8, CD14, CD19, CD56, Live/Dead near-IR CD25, CD27, CD45RA, CD95, CD127, CD194, CD195, CD197
Lymphoid Activation/Exhaustion Panel	CD3, CD4, CD8, CD14, CD19, CD56, Live/Dead near-IR CD152, CD223, CD226, CD244, CD272, CD279, CD366
Lymphoid Subset Panel	CD3, CD4, CD8, CD14, CD19, CD56, Live/Dead near-IR CD25, CD45RA, Tbet, GATA-3, RORγT, FoxP3

Table 3. Cytokine & Chemokine Detection Panels

Panel Name	Cytokine/Chemokines Detected
LUNARIS™ Human 11-Plex Cytokine Multiplex Kit	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, TNF-α, GM-CSF, IFN-γ
LUNARIS™ Human 11-Plex Chemokine Multiplex Kit	MCP-1, MIP-1α, MIP-1β, RANTES, Eotaxin, MIP-3β, MIP-3α, GROα, IL-8, IP-10, SDF-1
APRIL/BAFF Human ELISA Kit	APRIL, BAFF

6.3 GERIATRIC ASSESSMENT

It is well recognized that elderly patients are a heterogeneous population with varying physiological reserves and comorbidities that affect treatment outcomes. Geriatric assessment is an effective way to identify frailty in elderly cancer patients, and help predict for risk of toxicity from treatment in this population. Geriatric assessment involves systematic evaluation of various domains of functioning in the elderly, including ADLs/IADLs, medical comorbidities, cognition, nutrition and psychological state. There have been numerous validated models developed to evaluate frailty in older adults, particularly the International Myeloma Working group (IMWG) frailty score, which was shown to predict mortality and toxicity in elderly myeloma patients[1]. To our knowledge, the prognostic and predictive value of geriatric assessment has not been evaluated with elderly patients who are treated with daratumumab.

The original Balducci frailty score was among the first systems developed to identify frailty in oncology patients[15]. This score classified patients as being fit, vulnerable, or frail, based on a geriatric assessment that included age, ability to perform ADLs, comorbidity, and the presence of geriatric syndromes. A modified version of this score has been proposed which takes into account a patient's independence in ADLs, IADLs, comorbidities, and presence of geriatric syndromes. Notably, this does not include age as a criterion, but rather focuses on functional age rather than chronological age.

The International Myeloma Working group (IMWG) frailty score has been shown to predict mortality and toxicity in elderly myeloma patients[1]. Similar to the Balducci score, the IMWG frailty score is calculated using age, the Charlson comorbidity index, and ability to perform ADLs/IADLs. In patients classified as "fit," 3 yr overall survival was 84%, compared to 57% in patients classified as "frail".

The IMWG frailty score as well as a modified Balducci frailty score will be administered during screening and during cycle 2 day 22. These assessments will be used to stratify patients into fit, intermediate-fitness, and frail categories.

Geriatric assessment will be correlated with the following: Grade 3 or greater non hematologic adverse events, grade 3 or greater hematologic adverse events, discontinuation of the trial, dose reduction of lenalidomide or bortezomib and finally progression free survival.

Biomarkers may also predict for frailty and adverse outcomes in older patients. For example, the C-reactive protein (CRP) rise with increasing age and are associated with decreased walking speed and grip strength. Other molecular markers that have been found to be associated with clinical signs of frailty include D-dimer levels. These biomarkers will be obtained at screening and C2D22.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Patients can continue on treatment as part of this trial as long as they are benefiting from therapy or unacceptable toxicities. Patients with progressive disease on daratumumab during the first 2 months of therapy, will be allowed to receive the addition of lenalidomide or bortezomib. Progression beyond the first two months of therapy will result in the patients discontinuing treatment on the trial.

Patients who discontinue therapy on the trial for reasons other than progressive disease will continue to be monitored for progression until progressive disease or the start of another myeloma therapy. This can be performed via phone interview and review of records at least every 3 months.

The data to be collected at the time of treatment discontinuation will include the following:

- IMWG response assessment
- Assessment of adverse events

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy

- Significant study intervention non-compliance which in the opinion of the investigator places the patient at increased risk
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention (except during the first 2 months of therapy where the addition of lenalidomide or bortezomib would be allowed on the trial)
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive trial therapy for greater than 8 weeks.

The reason for participant discontinuation or withdrawal from the study will be recorded within the patient's medical record and OnCore and/or the Clinical Trial Management System (CTMS). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study; may not be replaced and are considered treatment failure per intent to treat.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The primary endpoint of this trial is overall response rate as assessed by the uniform response criteria of the international myeloma working group (appendix A)

- At screening, and day 1 of every cycle (except cycle 3) and cycle 2 day 22 and at the end of treatment, patients will have a serum protein electrophoresis with immunofixation, a 24h urine protein electrophoresis with immunofixation, as well as serum free light chain testing. These will be used for response assessments on these time points. If a 24 h urine protein electrophoresis is obtained within 7 days prior to cycle 1 day 1, it will not need to be repeated on cycle 1 day 1 and the screening value will be used for baseline.
- Compliance with 24h urine protein electrophoresis is a concern for many multiple myeloma trials due to the fact that obtaining 24h urine collection is a burden on patients. In addition, considering many patients enrolled on this study will be / are elderly and some may have incontinence or

other mobility issues that may make such a collection a difficulty; we anticipate some patients will not be able to obtain monthly 24h urine testing for protein electrophoresis. Patients will be reminded to collect a 24h urine for protein elctrophoresis prior to the appointment date by the trial coordinator. If despite these reminders, the patients was not able or did not provide a 24h urine collection for testing, the missing labortatory test will not be considered a deviation from the protocol.

- A serum b2microglobulin and LDH will be obtained at screening for risk stratification.
- A bone marrow biopsy and aspirate will be performed on screening, cycle 2 day 22, and end of treatment. EMMA testing will be performed using the bone marrow aspirates from these time points. The screening bone marrow assessment will include metaphase cytogenetics as well as standard myeloma FISH testing. In addition, patients who achieve a VGPR (if the remainder m spike is consistent with daratumumab interference) or CR at any point or better will undergo a bone marrow biopsy for histology (confirmation of CR) and MRD testing using NGS and by flow cytometry.
- A skeletal survey or FDG PET/CT will be performed on screening and at the end of treatment in the event of progressive disease. If PET CT or bone survery has been performed within 28 days of cycle 1 day 1 but prior to screening (per standard of care), it would not need to be repeated during screening
- Geriatric assessments will be performed on screening and cycle 2 day 22. This will be captured on the MM frailty eCRF
- Immune profiling will be performed on screening and cycle 2 day 22.

8.2 SAFETY AND OTHER ASSESSMENTS

The following assessments will be performed to evaluate the safety of this strategy

- **Physical examination**, **weight and ECOG performance status:** These are assessments are performed on screening, day 1 of every cycle and end of treatment. Height will only be measured on screening. Note that only baseline/screening height, weight, and performance status will be captured in the eCRF.
- **Review of the medical history:** This trial will focus on collecting notable comorbidities and geriatric syndromes (e.g. falls, incontinence, cognitive impairment) especially considering the geriatric / frailty assessment is dependent on this assessment
- **Vital signs** (e.g., temperature, pulse, respirations, blood pressure). Vitals are to be obtained on screening, day 1 of every cycle and end of treatment. Vitals signs will not be captured in the eCRF unless an adverse event is noted which would be captured in the AE log
- **Laboratory evaluations**. A complete blood count with differential, a complete metabolic profile and LDH will be obtained on screening, weekly during the first 2 cycles and every 2 weeks during cycles 3-6 and monthly after cycle 7. At screening, a type and screen will also be performed per standard of care for patients receiving daratumumab. Only the screening hematology and chemistry will be captured in the eCRF unless there is an adverse event which will be captured in the AE log
- **Assessment of adverse events.** Adverse event review and evaluation will be an ongoing process during the treatment phase of the trial. Patients will be followed for AE and SAE for 30 days after the discontinuation from the treatment phase of trial unless there is a treatment related AE which has not recovered to grade 1 or less.
- **Review of concomitant medications** : this will be an ongoing process and ~~will~~ concomitant medications will only be recorded in the eCRF if they are associated with an AE. Concomitant medications will only be reviewed at the time of clinic appointments for D1 of each cycle but not during laboratory appointments in between cycles.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

All AEs will be graded using the CTCAE 5.0 criteria.
For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to

concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (eg, the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (eg, the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate case report form (CRF). Information to be collected will include event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode when grade 3 or greater. All other intermittent AE will be reported as one episode using the highest grade.

All events beginning with start of study intervention until 30 days after the last day of study intervention will be reported. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All adverse events will be recorded through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Such reporting will be within 24 hours of knowledge of the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications, all concomitant medications, and medical treatment provided. The PI is responsible for evaluating all adverse events to determine whether criteria for "serious" as defined above are present. Adverse drug reactions that are serious, unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigator's Brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The Principal Investigator or designee shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug, as soon as possible, but no later than 7 calendar days after the sponsor's initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

8.3.7 EVENTS OF SPECIAL INTEREST

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

- Infusion reactions: ≥ grade 3

- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- Tumor lysis syndrome
- Other malignancies
- Intravascular hemolysis – all grades

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

8.3.8 SPECIAL REPORTING SITUATIONS

Although female participants in this study are of non-child bearing age (given requisite age > 65 years), a pregnancy in a female partner of male participant is a possibility. Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.
Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

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

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor in accordance with Moffitt policy.
- Any other UP will be reported to the IRB and to the DCC/study sponsor in accordance with Moffitt policy
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) in accordance with Moffitt policy.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems that impact the risk, benefits of the participation in the clinical trial will be reported to the patients and the decision to continue or discontinue trial therapy will be made by the patient and their treating physician. Patients who will continue on treatment will need to be re-consented with an informed consent that has the updated risk / unanticipated problem discussed.

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

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, a photograph should be obtained.

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

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Overall response rate (partial response and better) of the response adapted strategy using the uniform response criteria of the IMWG

- Secondary Efficacy Endpoint(s):

The proportion of patients who progression free at 1 and 2 years

Overall response rate (partial response or better) after 2 cycles of daratumumab

Proportion of patients who continue on daratumumab monotherapy after 2 cycles.

Proportion of patients who are without minimal residual disease (MRD-) using Next Generation sequencing (NGS)

The 2 year overall survival of this response adapted approach

Safety profile of subcutaneous daratumumab based therapy in older adults newly diagnosed multiple myeloma

Agreement between actual responses and responses as predicted by an Ex Vivo Mathematical Myeloma Advisor (EMMA)

9.2 SAMPLE SIZE DETERMINATION

The primary goal of the study is to evaluate the efficacy of daratumumab alone or in combination with lenalidomide or bortezomib. The primary endpoint is overall response rate (partial response and better) of the response adapted strategy using the uniform response criteria of the IMWG in older patients with newly diagnosed multiple myeloma. A patient who withdraws prior to the completion of cycle 2 at any

reasons other than the progression of disease or death is considered “non-evaluable” for efficacy and will be replaced. The overall response rate in these patients is 70%. From this historical data, we will consider overall response rate of ≤70% as not warranting further study. We will use overall response rate of ≥90% as a promising result to pursue further study. Simon’s minimax two-stage design [16][18][18][18][18]with 5% type I error rate and 10% type II error rate will be used[17]. Eighteen evaluable patients will be enrolled in the first stage. If 14 or more PR or better responses are noted as the best response to the response adapted therapy, additional 14 evaluable patients will be enrolled. If 27 or more patients achieve a PR or better among 32 evaluable subjects, the combination is deemed promising. If the regimen is actually not effective, there is a 5% probability of concluding that it is. If the regimen is actually effective, there is a 9.9% probability of concluding that it is not. The probability of early termination is 66.7% and 2.8% if the true overall response rate is 70% and 90%, respectively.

9.3 POPULATIONS FOR ANALYSES

- Safety Analysis Population: Patients who took at least one dose of daratumumab. This population will be used for the evaluation of safety of the study agent.

- Per-Protocol (PP) Population: A patient who withdraws prior to the completion of cycle 2 at any reasons rather than the progression of disease or death is considered “non-evaluable” for efficacy. PP population includes all evaluable patients and will be used for efficacy evaluation of daratumumab alone or in combination with lenalidomide or bortezomib.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Patient demographic and clinical characteristics will be summarized using descriptive statistics (frequency and proportion for categorical variables and mean, standard deviation, median and range for continuous variables). All toxicities will be listed for each patient and summarized per Safety Analysis Population. Data transformation may be considered to apply parametric analytic methods.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For the primary endpoint, the overall response rate of the response adapted strategy is estimated and is compared with historical efficacy data in old patients with newly diagnosed multiple myeloma. The overall response rate and its confidence interval will be calculated by using the Atkinson and Brown method[18][20][20]. This confidence interval takes into account the nature of Simon’s two-stage design[17].

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINTS

- Progression-Free Survival (PFS): Time from start of the treatment to death of any cause, disease progression or relapse, or the date of last follow-up, whichever comes first. The PFS will be estimated by the Kaplan-Meier method and 95% confidence interval (CI) will be computed by complementary log-log transformation. The 1 and 2 year PFS and 95% CIs will be reported.

- Overall Survival (OS): Time from start of the treatment to death of any cause or the date of last follow-up, whichever comes first. The OS will be estimated by the Kaplan-Meier method and 95% confidence interval will be computed by complementary log-log transformation. The 2 year OS and 95% CI will be reported.

- Overall response rate after 2 cycle of daratumumab will be estimated and the 95% confidence interval will be computed by the Clopper-Pearson method.
- Proportion of patients who are without minimal residual disease using Next Generation Sequencing (NGS) will be estimated and the 95% confidence interval will be computed by the Clopper-Pearson method.
- The performance of EMMA will be evaluated by estimating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the receiver operating characteristic (AUC) curve. The accuracy of the EMMA will be reported and 95% CI will be computed by the Clopper-Pearson method.
- Correlation between the grade 3 and greater non hematologic and hematolgic adverse events and frailty assessment.

9.4.4 SAFETY ANALYSES

All toxicities will be listed for each patient and summarized for each study arm (daratumumab alone + dexamethasone (Arm A), daratumumab + dexamethasone + lenalidomide (Arm B), daratumumab + dexamethasone + bortezomib (Arm C)).

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Patient demographic and clinical characteristics will be summarized using descriptive statistics (frequency and proportion for categorical variables and mean, standard deviation, median and range for continuous variables).

9.4.6 PLANNED INTERIM ANALYSES

Eighteen evaluable patients will be enrolled in the first stage. The study will be early terminated for futility if ≤13 patients achieve a PR or better response. If 14 or more PR or better responses are noted, additional 14 evaluable patients will be enrolled. The interim analysis will occur after 18 patients have received at least 4 cycles of therapy. if the requisite number of response has already been met, prior to the completion of 4 cycles by all 18 evaluable patients, enrollment would continue. However if it is felt that the requisite number of response is not met (13 or less responders), the enrollment would be halted until all 18 evluables patients have received 4 cycles of therapy.

9.4.7 SUB-GROUP ANALYSES

The overall response rate, OS, and PFS will be estimated for each study arm (daratumumab alone + dexamethasone (Arm A), daratumumab + dexamethasone + lenalidomide (Arm B), daratumumab + dexamethasone + bortezomib (Arm C)). However, no formal comparisons between arms will be made.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Moffitt cancer center.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

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8137458212
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10.1.5 SAFETY OVERSIGHT

Serious Adverse Events: Serious Adverse Events (SAEs) from this protocol will be reported concurrently to the IRB and the study sponsor. The Protocol Monitoring Committee (PMC) will review these SAEs in accordance with the protocol-specific DSMP. The data and safety plan will define dose limiting toxicities, rules for escalation of dose, and criteria for stopping the trial and defining the Maximum Tolerated Dose (MTD) according to rules set forth by this protocol. This trial will be continuously monitored by the PI and the research team and reviewed at biweekly Myeloma Research Group meetings. Safety and monitoring reports will be submitted to the PMC after completing each odd numbered dose level (ie, 1, 3, 5, etc.) or more frequently if requested by the PMC. A final safety and monitoring report will be submitted to the PMC within three months of defining the MTD. This protocol will be subject to periodic internal audits based on risk or as recommended by the PMC.

10.1.6 CLINICAL MONITORING

Moffitt's Internal Monitors will periodically monitor regulatory documents and case report forms according to the protocol specific clinical monitoring plan. Monitoring will include review of data for accuracy, completeness, and source verification, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and

reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data will be captured in OnCore and/or Moffitt's electronic Clinical Trials Management System. For each subject enrolled, the electronic CRF must be completed by the assigned data manager or other authorized study staff. Any paper forms should be typed or filled out indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those subjects who fail to complete the study. If a subject stops dosing or terminates from the study, the dates 64 and reasons must be noted on the CRF. If a subject terminates from the study because of a DLT, thorough efforts should be made to clearly document the outcome.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into <specify name of data capture system>, a 21 CFR Part 11-compliant data capture system provided by the <specify Data Coordinating Center>. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to the Protocol Monitoring Committee. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP. Deviations must be entered into the Clinical Trials Management System (CTMS).

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting Rachid Baz, MD

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Center (IC) has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMS	Centers for Medicare and Medicaid Services
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C reactive protein
CTMS	Clinical Trial Management System
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
EMMA	Ex Vivo Mathematical Myeloma Advisor
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NIH	National Institutes of Health
NIH IC	NIH Institute & Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
5.0	08/12/2019	Title Page: tracked from version 4 to 5 Header : Tracked to version 5 dated 08/12/2019 Appendix C: Section 4.1: age of inclusion changed from 70 to 65 Page 3: #12 already shows Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods added; all references in Protocol amended to Appendix C	
6.0	9/9/2019	Title Page: tracked from version 5 to 6 Header : Tracked to version 6 dated 9/9/2019 Addition of section 13.4 and 13.5, Senior Adult Supplement Screening Questionnaire, The Mini Cog Evaluation Added language in Appendix C	
7.0	12/19/2019	Title Page: tracked from version 6 to 7 Eligibility of Patients : ECOG Performance status- typo updated from “0 or 2” to “0 – 2 Inclusion Criteria : Inclusion # 6 – ECOG Performance status-typo updated from “0 or 2” to “0 – 2 Added a 7 day window for cycle 3 day 1 Added NTC Number	
8.0	1/29/2021	Title page tracked from version 7 to 8 Updated header	

		Added Appendix D for definition of myeloma defining event	This was recommended at monitoring visit
		Allow bortezomib maintenance after 8 cycles of bortezomib based therapy per treating physician discretion. Allow holding bortezomib for some grade 2 adverse event per treating physician recommendations	This is to confirm with standard practice as bortezomib for bortezomib maintenance and therapy
		Allow hormonal therapy inclusion as concomitant therapy	This is not expected to interfere with myeloma therapy
		Updated visit windows for cycle 3 and beyond	For patient convenience
		Allowed use of pre-screening standard of care PET CT or skeletal survey if done within 28 days of starting therapy	PET CT or skeletal survey often performed as part of standard of care do not need to be repeated within 28 days
		Allowed avoiding to repeat a 24h urine protein electrophoresis for cycle 1 day 1 if performed withing 7 days during screening	24h urine collection is an inconvenient test for patients and a repeat within 7 days is not clinically needed
		Clarified the time when a bone marrow biopsy to confirm CR is needed for patients in VGPR in case of suspected daratumumab interference with immunofixation	This is per standard of care
		Added type and screen on screening	This is per standard of care
		Omitted phosphorus form routine chemistry labs to be performed	This is not needed for the study and can be ordered if clinically indicated
		Updated wording on FDA approval of SC daratumumab in the protocol and use of commercial “DARZALEX FASPRO” supplied by Janssen	Daratumumab SC was approved in 5/2020 and Janssen will be providing DARZALEX FASPRO
		Updated senior adult oncology questionnaire form version number	A new version is available. No change in content
		Corrected various typos	

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12 APPENDIX A: IMWG RESPONSE CRITERIA

Response Subcategory	Response Criteria[a]
Stringent complete response (sCR)*†	• Negative immunofixation on the serum and urine (regardless of whether disease at baseline was measurable on serum, urine, both, or neither) and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[b] and • Normal FLC (free light chain) ratio and • Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c] or 2 to 4 color flow cytometry
Complete response (CR)*†	• Negative immunofixation on the serum and urine (regardless of whether disease at baseline was measurable on serum, urine, both, or neither) and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[b] and • For subjects in whom the only measurable disease is by serum FLC levels, a normal FLC ratio** is also required.
Very good partial response (VGPR)*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-component plus urine M component < 100 mg per 24-hr For subjects in whom the only measurable disease is by serum FLC levels, VGPR is defined as: • ≥ 90% decrease in the difference between involved and uninvolved FLC levels
Partial response (PR)	• ≥ 50% reduction of serum M-protein and • Reduction in 24-hr urinary M-protein by ≥ 90% or to < 200 mg per 24 hr ○ If the serum and urine M-protein are unmeasurable,[d] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. • ≥ 50% reduction in the size of soft tissue plasmacytomas is also required, if present at baseline.
Minimal response (MR)	• 25% – 49% reduction of serum M-protein and • 50% – 89% reduction in 24-hour urinary M-protein and • 25% – 49% reduction in size of soft tissue plasmacytomas, if present at baseline, and • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable disease (SD)[e]	Not meeting criteria for sCR, CR, VGPR, PR, MR or progressive disease (PD).

a. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

b. Confirmation with repeat bone marrow biopsy not needed.

c. Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of > 4:1 or < 1:2.

d. Measurable disease is defined as meeting at least one of the following measurements:

Serum M-protein≥ 1 g/dL or

Urine M-protein ≥ 200 mg/24 hr or

Serum FLC assay with an involved FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal

e. Not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates.

Notes:

*** Clarification to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels:**

CR in such subjects is defined as a normal FLC ratio of 0.26 – 1.65 in addition to CR criteria listed above. VGPR in such subjects is defined as a > 90% decrease in the difference between involved and uninvolved free light chain FLC levels.

** Serum and urine M-protein testing is required to fulfill requirements of VGPR and CR categories regardless of whether disease at baseline was measurable on serum, urine, both, or neither.

† For those subjects with negative or low SPEP (≤0.2 g/dL) and suspected daratumumab interference, a reflex assay using anti-idiotype antibody will be utilized to confirm daratumumab interference and rule out false positive immunofixation. Subjects who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR. Subjects with a non IgG kappa multiple myeloma who have an IgG kappa monoclonal protein on immunofixation will be assumed to have daratumumab interference in the absence of an assay.

Progressive disease is defined as below:

Increase of > 25% from lowest response value in any one or more of the following:

- Serum M-component and/or (the absolute increase must be > 0.5 g/dL). For progressive disease, serum M-component increases of >1 gm/dL are sufficient to define relapse if starting M-component is >5 g/dL.
- Urine M-component and/or (the absolute increase must be > 200 mg/24 h)
- Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL
- Bone marrow plasma cell percentage; the absolute percentage must be > 10%
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas

- Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

All responses must be confirmed by repeat testing within 6 weeks for the definition of a best response and progression.

13 APPENDIX B: IMWG GERIATRIC ASSESSMENT

13.1.1 ACTIVITIES OF DAILY LIVING (ADL) AND INTRUMENTAL ACTIVITY OF DAILY LIVING (IADL)

The ADL scale includes six items (bathing, dressing, toileting, transferring, continence, and feeding), with a score for each item ranging from 0 (unable to perform the activity) to 1 (able to perform the activity). Total score ranges from 0 to 6 (0 = completely dependent; 6 = completely independent). The IADL scale includes eight items (ability to use the telephone, shopping, cooking, housekeeping, doing laundry, taking own medication, using transportation, and handling finances), with a score for each item of 0 (low function, dependent) or 1 (high function, independent). The total score ranges from 0 to 8 (0 = completely dependent; 8 = completely independent).

Score	ADL	IADL
0-1	Bathing	Ability to use the phone
0-1	Dressing	Shopping
0-1	Toiletting	Food preparation
0-1	Transferring	Housekeeping
0-1	Continence	Laundry
0-1	Feeding	Mode of transportation
0-1		Responsible for own medications
0-1		Responsible for own finances

13.1.2 CHARLSON COMORBIDITY INDEX (CCI)

Assigned Weight	Condition(s)
1	Myocardial infarction, congestive heart failure, peripheral arterial disease, cerebrovascular disease (includes transient ischemic attack), dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease (no portal hypertension), diabetes without end organ damage
2	Hemiplegia, moderate to severe renal disease, diabetes with organ damage, tumor without metastasis (within 5 years), leukemia, lymphoma
3	Moderate to severe liver disease
6	Metastatic solid tumor, Acquired Immunodeficiency Syndrome (AIDS)

13.1.3 IMWG FRAILTY SCORING

Condition	Score
Age	
75 or less	0
76-80	1
>80	2
ADL	
>4	0
4 or less	1
IADL	
>5	0
5 or less	1
CCI	
1 or less	0
2 or more	1

Score	Frailty Category	Estimated 3 years Overall Survival
0	Fit	84%
1	Intermediate fitness (unfit)	76%
2 or more	Frail	57%

13.1.4 TIMED UP AND GO (GAIT SPEED)

Gait speed can be evaluated as previously described by Liu M, and others, where in brief: from a standing start, participants are asked to walk at a usual pace for 4 meters using distinct landmarks and with speed recorded in meters per second, using a stopwatch (Liu M, et al. Blood 2019). This was found to be a useful marker of frailty.

13.1.5 SENIOR ADULT ONCOLOGY CLINIC QUESTIONNAIRE

We will employ the senior adult oncology clinic questionnaire as part of the geriatric assessment. The questionnaire is show below.

SENIOR ADULT SUPPLEMENT SCREENING QUESTIONNAIRE (SAOP3)

Form #16952-1-004 5/19

1. If it was necessary, is there someone who could help take care of you [ ] Yes [ ] No

2. Do you feel sad more days than not [ ] Yes [ ] No

3. Have you lost interest in things you used to enjoy (hobbies, food, sex, being with friends / family)

[ ] Yes [ ] No

4. On a scale of 1 to 10, rate your ***present*** quality of life (10 is the best, 1 is the worst)

[ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] 8 [ ] 9 [ ] 10

5. On a scale of 1 to 10, rate your ***present*** overall health (10 is the best, 1 is the worst).

[ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5 [ ] 6 [ ] 7 [ ] 8 [ ] 9 [ ] 10

6. Activities of Daily Living / Instrumental Activities of Daily Living (ADL/IADL

	(please check one for each line)		
a. Do you use a cane or a walker?	[ ] Yes	[ ] Occasionally	[ ] No
b. Do you need help to get out of bed / chair?	[ ] Yes	[ ] Occasionally	[ ] No
c. Have you tripped or fallen in the past year?	[ ] Yes		[ ] No
d. Can you shower or bathe yourself completely?	[ ] Yes	[ ] Yes, but with help	[ ] No
e. Can you dress yourself completely?	[ ] Yes	[ ] Yes, but with help	[ ] No
f. Can you feed yourself?	[ ] Yes	[ ] Yes, but with help	[ ] No
g. Are you able to drive?	[ ] Yes	[ ] Have never driven	[ ] No
h. Are you able to prepare your own meals?	[ ] Yes	[ ] Yes, but with help	[ ] No
i. Are you able to go shopping?	[ ] Yes	[ ] Yes, but with help	[ ] No
j. Can you take care of your finances?	[ ] Yes	[ ] Yes, but with help	[ ] No
k. Can you use a telephone?	[ ] Yes	[ ] Yes, but with help	[ ] No
l. Do you remember to take your medicines?	[ ] Yes	[ ] Yes, but with help	[ ] No
m. Do you have problems holding your urine or stools (more than small leaks controlled with a pad)?	[ ] Yes	[ ] Occasionally	[ ] No

7. Have you lost 5 or more pounds in the past 6 months without dieting? [ ] Yes [ ] No

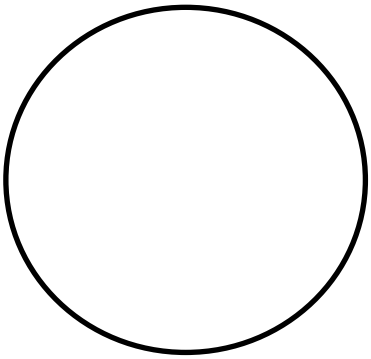
8. Has your appetite decreased in the last 3 months? [ ] Yes [ ] No

9. Has there been a change in the ***types*** of food you are able to eat? [ ] Yes [ ] No

10. Are you able to pay for your prescription medications? [ ] Yes [ ] No

11. Do you feel you are sleeping well? [ ] Yes [ ] No

The Mini Cog Evaluation ™



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1. Insruct the patient to listen carefully and repeat the following words: [ ] Apple [ ] Watch [ ] Penny

2. Instruct the patient to draw a clock and put in all the number where they go. then instruct the patient to place the hands of the clock to represent the time “forty five minutes past ten o’clock”

3. Ask the patient to repeat the three words previously given: _____ _____ _____

Scoring:

Number of correct items recalled : _____ (if 3, then normal. Stop. If 0, then cognitive impairement. Stop)

If 1-2, is clock drawing abnormal? [ ] Yes (cognitive impairement) [ ] No (normal)

Psychosocial items 1-3: if at least one **Yes** response, then consult Social Work
ADL / IADL mobility items (6a-6c): if at least two **Yes** responses, then consult Outpatient Physical therapy ADL / IADL ietms 6c-6m: if at least one **No** response, then consult Outpatient Occupational therapy
Quality of life (QOL) and self rate health items (4-5), if score less then 8, then consult Social Work
Nutrition items (7-9): if at least two **Yes** responses, then consult Outpatient Nutrition
Mini-Cog: MMSE <24 if cognitive impairement, then consult Outpatient Occupational therapy or Speech Path
Number of Medications greater than 5, then consult Pharmacy
If **No** to #10, refer to Social Work or Patient Financial Services
If **No** to #11, administer Pittsburgh Sleep Quality Index (PSQI) for further referral
Geriatric Depression Scale Score: _____, if Score greater than 5, the consult Behavioral Medicine
Referral: [ ] Yes [ ] No | To:

14 APPENDIX C: RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore, daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the participant becomes pregnant while taking this drug, the participant should be informed of the potential risk to the fetus.

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during and for 3 months after cessation of daratumumab treatment.

While this study will enroll participants over the age of 65 years, women who are enrolled on the study are not of childbearing potential. Female participants must agree not to become pregnant while enrolled in this study. In addition, pregnant or breastfeeding women are not allowed to participate. For men, the effect of daratumumab on sperm is unknown.

Men must adhere to the following.

- Participants must agree to the use of independent highly effective methods of contraception during the study (including during dose interruptions), and for 4 weeks following discontinuation of lenalidomide, and if receiving daratumumab, for 3 months after the last dose
- A man, even if he has undergone a successful vasectomy, who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (ie, latex or synthetic condom with spermicidal foam/gel/film/cream/suppository)
- A man who is sexually active with a woman who is pregnant must use a latex or synthetic condom.
- A man must agree not to donate sperm

Because of the embryo-fetal risk of lenalidomide, all subjects who are receiving this agent, must adhere to the lenalidomide REMS program that can be accessed at *http://www.revlimidrems.com/*

15 APPENDIX C: INTERNATIONAL MYELOMA WORKING GROUP UPDATED CRITERIA FOR THE DIAGNOSIS OF MULTIPLE MYELOMA

Definition of symptomatic multiple myeloma

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

Myeloma defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
- Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL)
- Anemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡

Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage* ≥60%
- Involved:uninvolved serum free light chain ratio§ ≥100
- >1 focal lesions on MRI studies¶

PET-CT=^{18}F-fluorodeoxyglucose PET with CT.

*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

†Measured or estimated by validated equations.

‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.

¶Each focal lesion must be 5 mm or more in size.

Adapted from Rajkumar et al. Lancet Oncol. 2014 Nov;15(12):e538-48.

APPENDIX D: Worksheet for Revised International Staging System (R-ISS) and Classification of FISH Findings (Adapted from Palumbo et al J Clin Oncol; 2015; 33(26):2863-9)

FISH (circle all that applies):

Deletion 13	YES	NO
Deletion 17	YES	NO
Amp/ Gain 1q	YES	NO
Deletion 1p	YES	NO
T(11;14)	YES	NO
T(4;14)	YES	NO
T(14,16)	YES	NO
Hyperdiploid	YES	NO

CA by iFISH

High risk Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk No high-risk CA

ISS: _____

B2microglobulin:_____

Albumin: _____

ISS stage

I Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II Not ISS stage I or III
III Serum β_2-microglobulin ≥ 5.5 mg/L

LDH: _____

LDH

Normal Serum LDH < the upper limit of normal
High Serum LDH > the upper limit of normal

R-ISS: _____

R-ISS stage

I ISS stage I and standard-risk CA by iFISH and normal LDH
II Not R-ISS stage I or III
III ISS stage III and either high-risk CA by iFISH or high LDH