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Evaluating Mechanisms of Immunomodulator Sensitivity and Resistance in Multiple Myeloma

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Mayo Clinic Cancer Center

Evaluating Mechanisms of Immunomodulator Sensitivity and Resistance in Multiple Myeloma

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Drug Availability:
Commercial Agents: Lenalidomide, Pomalidomide, and Dexamethasone

√Study contributor(s) not responsible for patient care

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Protocol Resources

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*No waivers of eligibility allowed

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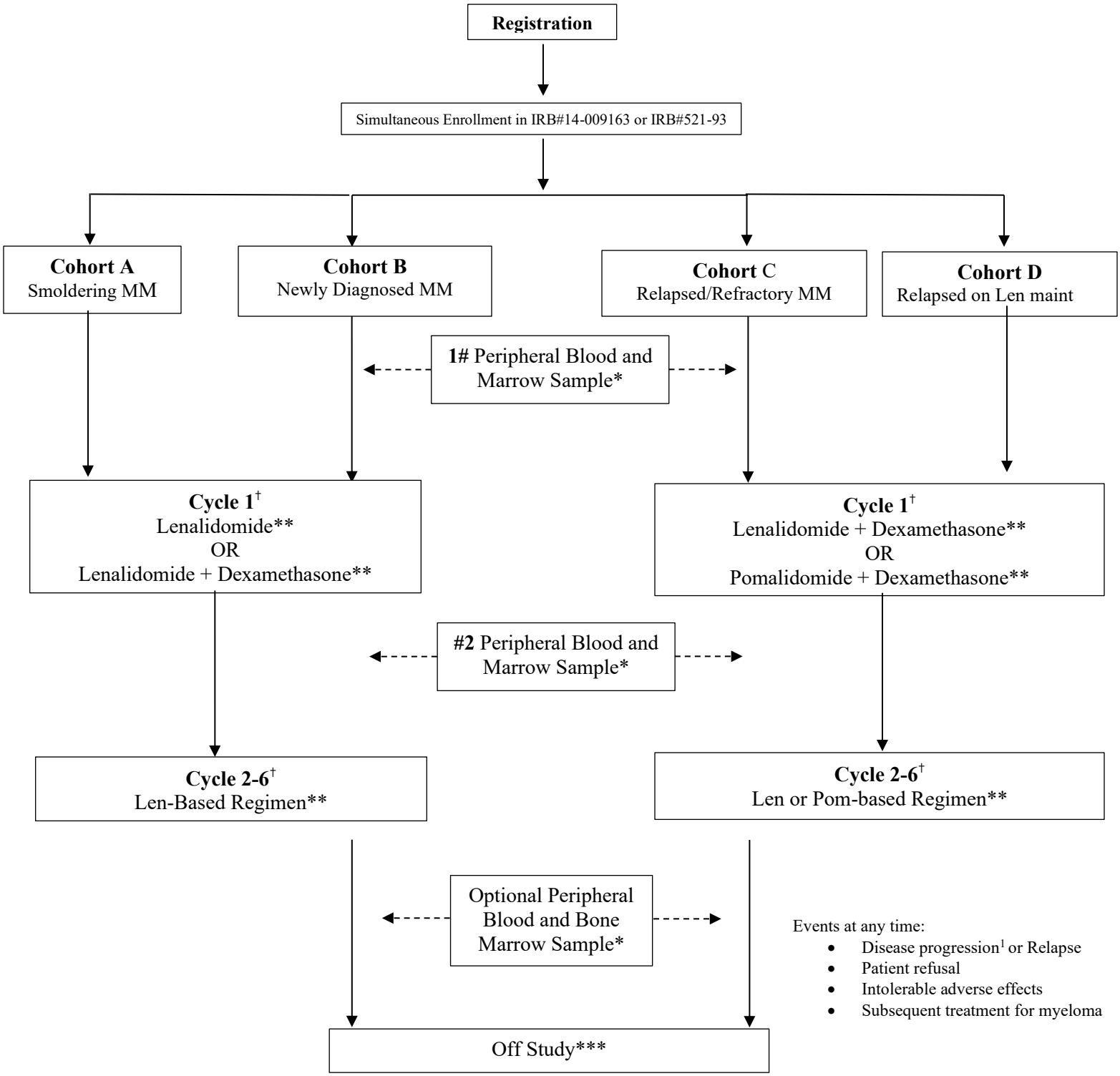
Schema



*Sample collection under IRB#14-009163, IRB#919-04, or IRB#521-93

**Dosing and regimen as per section 7

***Patients who discontinue treatment before completing 6 cycles for any reason will go off study (No SFU/CFU).

†Cycle 1 = 21. Cycles 2 – 6 = 28 days

Generic name: Lenalidomide Brand name(s): Revlimid Mayo Abbreviation: Availability: Commercial	Generic name: Pomalidomide Brand name(s): Pomalyst Mayo Abbreviation: Availability: Commercial	Generic name: Dexamethasone Brand name(s): Mayo Abbreviation: Availability: Commercial

1.0 Background

Multiple myeloma (MM) is a clonal plasma cell malignancy that tends to affect the older patient with a median age at onset of 65-70 years and a slight male predominance. The American Cancer Society estimates that about 30,330 new cases of MM will be diagnosed in 2016, and about 12,650 patients will die of the disease.(*1*) Patients with MM can experience bone pain, bone fractures, fatigue, anemia, infections, hypercalcemia and kidney problems.(*2*) Treatment options are based on the patient's disease status. Standard treatments for MM include combination chemotherapy regimens containing proteasome inhibitors (PIs) such as bortezomib and carfilzomib, and/or immunomodulatory drugs (IMiDs), such as lenalidomide and pomalidomide, in combination with corticosteroids.(*3*) Alkylating agents such as melphalan and cyclophosphamide are also active in MM.(*3*) Patients under the age of 75, who are free from significant comorbidities, are often treated with myeloablative chemotherapy and/or radiation, followed by autologous stem cell transplantation (ASCT).(*3*) These treatments have improved outcomes of patients with MM in recent years, both in the relapsed setting as well as at diagnosis.(*4*)

However, despite considerable improvements in therapy, MM relapses remain inevitable and mostly incurable making it uniformly fatal with a median overall survival of around 8 years.(*5*) This is because MM cells actively evolve to develop resistance mechanisms against the cytotoxic effects of therapies that they are exposed to eventually leading to the exhaustion of all therapeutic options. In general, MM patients will receive an average of 4 to 8 different regimens during their lifespan utilizing agents such as proteasome inhibitors (e.g., bortezomib, ixazomib and carfilzomib), anti-CD38 monoclonal antibodies (e.g., daratumumab and isatuximab), immune modulatory agents (e.g., lenalidomide and pomalidomide), etc.(*5*) Currently, these aforementioned highly effective drug combinations used are beset with a various degrees of toxicity that precludes long-term therapy and also can affect the quality of life metrics. Furthermore, we are currently unable to reliably predict in advance whether a particular therapy would be effective or not until after administering it to a patient. This exposes patients to potential side effects from treatments that may not be beneficial in their case. In order to continue the pursuit of improving the overall survival and quality of life of MM patients, it is critical that we identify predictive biomarkers of response to therapies that will produce deep and durable remissions while at the same time alert patients and physicians of therapies that are unlikely to be successful.

1.1 Immunomodulators (IMiDs) as effective therapies in MM

The immunomodulatory drugs or IMiDs include thalidomide, lenalidomide and pomalidomide. These drugs have contributed to improvement in the overall survival of patients with MM. These drugs work through a variety of mechanisms due to its pleiotropic effects on multiple myeloma cells and the remainder of the cells associated with the immune system. IMiDs are widely used as induction therapy for both transplant eligible and ineligible patients, in the post-transplant maintenance setting, and for relapsed/refractory disease. As such, they remain the backbone of therapy for both newly diagnosed and relapsed disease.

Lenalidomide: The initial phase I study determined the maximal tolerated dose to be 25 mg (*6*). In terms of response rates, in the patients previously treated, studies revealed overall response rates of 48–61% and 46–57% in which most patients were previously treated with thalidomide(*7-9*). In the newly diagnosed setting, lenalidomide with dexamethasone was found to have an overall response rates of 68–91%..(*10, 11*) As a result, this regimen has replaced the use of thalidomide/dexamethasone as one of the most commonly used induction regimens in the United States. However, the administration of lenalidomide with dexamethasone changed when a study

comparing “high-dose” dexamethasone (40 mg days 1–4, 9–12, 17–20 of a 28-day cycle) to “low-dose” dexamethasone (40 mg days 1, 8, 15, 22 of a 28-day cycle) in combination with lenalidomide revealed a better one-year overall survival rate with an improved side effect profile for the low-dose weekly dexamethasone(*11*). This weekly dosing of dexamethasone is now routinely used in almost all myeloma regimens. More recently, the triplet combination of lenalidomide, bortezomib, and dexamethasone(*12*) has become a standard of care of newly diagnosed patients as it was found to provide a better progression free survival and overall survival compared to just lenalidomide and dexamethasone. In the post-transplant maintenance setting, lenalidomide is also widely used. Several randomized phase III studies have been performed, all of which have demonstrated significant PFS benefit with lenalidomide (*13-15*) including the CALGB 100104 study which revealed a significant OS benefit (*13*). A recent meta-analysis of the three studies assessing maintenance lenalidomide post-transplant confirmed an OS benefit(*16*).

Pomalidomide: This third generation IMiD was approved for the treatment of relapsed/refractory myeloma in 2013 for patients who had received at least two prior regimens including lenalidomide and bortezomib. This agent has only been evaluated in the previously treated setting. In one phase II study, the combination of pomalidomide and dexamethasone where the pomalidomide was dosed at 2 mg daily had a 63% overall response rate including 40% ORR in lenalidomide-refractory patients and 37% ORR in thalidomide-refractory patients(*17*). In another study which included only lenalidomide-refractory patients, the overall response rate was 47%(*18*). An alternative dosing strategy of 4 mg daily for 21 out of 28 days was also explored and the ORR was 35–42% (*19, 20*).

1.2 Rationale for the current trial

Current treatment regimens in both the upfront and relapsed settings have trended towards utilizing combination therapies that include a combination of an IMiD with proteasome inhibitors and/or monoclonal antibodies(*21, 22*). This is largely due to the results of several phase III clinical trials demonstrating the overall benefit of three-drug regimens (triplets) containing IMiDs and proteasome inhibitors or IMiDs and monoclonal antibodies over two-drug regimens (doublets) containing IMiDs alone with dexamethasone in terms of their depth and duration of hematological response. However, some patients within these clinical trials as well as in real-world clinical practice may derive equal depth and duration of therapeutic response to two-drug regimens (doublets) containing IMiDs alone with dexamethasone compared to triplets. At this time, our gap in knowledge prevents us from *apriori* identifying those patients who can be spared the physical and financial toxicity of adding the additional third or fourth agent such as proteasome inhibitors and/or monoclonal antibodies to an IMiD and dexamethasone. Being able to develop and validate biomarkers capable of filling this fundamental gap of knowledge could have practical implications to the clinical care of patients with MM. **As such, this study will provide the possibility of obtaining biospecimens from untreated smoldering MM and MM patients as well as previously treated MM patients pre- and post-treatment with one cycle of therapy containing only an IMiD and dexamethasone.**

Furthermore, it has been long hypothesized that there may be a differential response to IMiDs for patients belonging to African American (AA) race. Small studies have suggested that AA patients may have a better response to IMiDs than whites but receive a lesser access to these agents. This has led to the need for a more definitive testing to develop an efficacy profile as well as biomarker identification which may help predict the differences in response among AA and white patients with MM.

2.0 Goals

2.1 Primary Goal

To determine response rates (>=PR) of prospectively treated MM patients with one cycle of therapy containing a combination of an immunomodulator and dexamethasone.

2.2 Secondary Goals

1. To identify biomarkers that predict response rates of untreated smoldering MM and MM patients to a combination of an immunomodulator and dexamethasone.
2. To compare response rates of MM among AA and white patients to a combination of an immunomodulator and dexamethasone.
3. To establish correlation of biomarkers in treated MM patients with the combination of an immunomodulator and dexamethasone to the depth of hematological response observed in new or previously treated patients.

3.0 Registration Patient Eligibility

3.1 Registration - Inclusion Criteria

3.11 Age ≥18 years

3.12 **Cohort A:** Patient must have untreated smoldering multiple myeloma which is defined by the presence of 10% or more but less than 60% clonal plasma cells in the bone marrow and the absence of any of the following myeloma related symptoms or laboratory and radiographic abnormalities: anemia, hypercalcemia, renal insufficiency, hypercalcemia, serum free light chain ratio of greater than 100 or more than one focal marrow multiple myeloma lesion on MRI imaging.

Cohort B: Patient must have newly diagnosed myeloma requiring treatment and no prior therapies

Cohort C: Patient must have relapsed or refractory multiple myeloma with at least one prior therapy for their multiple myeloma but not refractory to all IMiDs

Cohort D: Patient must have relapsed or refractory multiple myeloma with Lenalidomide as part of a maintenance regimen as their most recent therapy

3.13 Measurable disease as defined in section 11.0

3.14 Provide written informed consent.

3.15 Patient must be considered for treatment with an IMiD containing regimen.

3.16 ECOG Performance Status (PS) 0, 1, 2 or 3 (Appendix I).

3.17 The following laboratory values obtained ≤14 days prior to registration:

- Hemoglobin ≥7.0 g/dL
- Absolute neutrophil count (ANC) ≥1000/mm^3
- Platelet count ≥50,000/mm^3

- Total bilirubin ≤1.5 x upper limit of normal (ULN) unless due to Gilbert's syndrome, in which case the direct bilirubin must be ≤1.5 X ULN.
- Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤3 x ULN (≤5 x ULN for patients with liver involvement)
- PT/INR/aPTT ≤1.5 x ULN OR if patient is receiving anticoagulant therapy and INR or aPTT is within target range of therapy
- Calculated creatinine clearance ≥45 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

3.18 Negative pregnancy test done ≤7 days prior to registration, for persons of childbearing potential only.

NOTE: If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.19a Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19b Willingness to provide mandatory blood and bone marrow specimens for correlative research (see Section 14.0).

3.19c Willing to follow the requirements of the Pomalyst® REMS program

3.2 Registration - Exclusion Criteria

3.21 An agent that has known genotoxic, mutagenic and teratogenic effects:
- Pregnant persons
- Nursing persons
- Persons of childbearing potential who are unwilling to employ adequate contraception

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy.

3.24 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.25 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.26 History of myocardial infarction ≤6 months.

4.0 Test Schedule

Tests and procedures	Prior to registration		Active Monitoring Phase			
	≤28 days	≤14 days	Prior to Day 1 Cycle 1	Prior to Day 1 Cycle 2	Prior to Day 1 Cycles 3-6	End of Treatment
Window				±3 days	±3 days	±7 days
Complete Medical History		X				
Physical exam, Wt, PS		X	X[3]	X	X	X
Adverse event assessment		X		X	X	X
Pregnancy test[1]		X				
Height		X				
Hematology group: CBC with 5-part differential		X	X[3]	X	X	X
Chemistry group to include serum creatinine, calcium, T.Bili, D. bili, AST, and ALT		X	X[3]	X	X	X
LDH, Beta-2-microglobulin, Plasma cell assessment		X	X[3]			
PT/PTT/INR		X				
TSH		X				
Electrophoresis of serum and urine		X	X[3,5]	X[5]	X[5]	X[5]
Immunofixation or mass fixation of serum and urine		X		X[7]	X[7]	X[7]
Affected Serum Immunoglobulin[2]		X	X[3]	X	X	X
Serum Immunoglobulin free light chain		X	X[3]	X	X	X
WBLDCT[3] or PET/CT	X			X[3]	X[3]	
Bone marrow aspirate and biopsy	X					
Patient Medication Diary (Appendix II)			X	X	X	
Research bone marrow sample[R]	X			X[6]		X[4]
Research blood sample[R]	X			X[6]		X[4]

Cycle 1 = 21
Cycles 2-6 = 28 days
Footnotes on following page:

1. For women of childbearing potential only. Must be done ≤7 days prior to registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required
2. Affected immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if patient "non-secretory" or if patient has no heavy chain, i.e. light chain myeloma. Affected immunoglobulin is required after baseline only if it used for disease monitoring instead of SPEP (e.g. IgA myeloma).
3. Baseline then only if clinically indicated.
4. Optional BM sample submission for patients who discontinue treatment due to disease progression or relapse, intolerable AEs, patient refusal, subsequent treatment for myeloma.
5 Urine Electrophoresis required only if used to assess disease response
6 Bone marrow aspirate done at the end of Cycle 1 (prior to cycle 2) will be paid for by research.
7. Immunofixation (IF) only needed in absence of M-Spike to document CR or SCR

R Collected as part of the IRB# 521-93, IRB# 14-009163 and/or IRB# 919-04

4.1 Survival Follow-up

Once a patient completes 6 cycles of therapy and/or is off study due to any reason, no further clinical and survival follow up is required.

5.0 Grouping Factor

5.1 Multiple Myeloma Cohort: Cohort A (Smoldering MM), Cohort B (Newly Diagnosed MM), Cohort C (Relapsed/Refractory MM) and Cohort D (Relapsed on Len maintenance).

6.0 Registration Procedures

6.1 **Registration:**

6.21 Registering a patient

To register a patient, access the Mayo Clinic Research Registration Application web page. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, call Research Site Management at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the Mayo Clinical Office of Clinical Trials web page (https://www.mayo.edu/research/centers-programs/center-clinical-translational-science/offices/office-of-clinical-trials/research-registration-application) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact Mayo Clinic Research Site Management at (507) 284-2753. If the patient was fully registered, the Research Site Management staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Verification of materials

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with Research Site Management (fax: 507-284-0885 or email random01@mayo.edu). If the necessary documentation is

not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Correlative Research

6.41 Mandatory

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19b and 14.0).

6.5 Treatment start

Treatment cannot begin prior to registration and must begin ≤28 days after registration.

6.6 Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.7 Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

7.1 Treatment Schedule

Cohort A and B Cycle 1

Treatment medication table. Patient may receive Lenalidomide OR Lenalidomide + Dexamethasone.

Agent	Dose Level	Route	Day	Re Rx
Lenalidomide	25 mg*	Oral	Cycle 1: Day 1-14	Cycle 1: 21 days
Dexamethasone	40 mg**	Oral	Cycle 1: Day 1 ,8, ,15	Cycle 1: 21 days

Cycle 1 length = 21 days

* Starting dose will be determined as per the creatine clearance below (see 7.12)

**The dose of dexamethasone used can be determined by the treating physician and omitted if needed.

Cohort C and D Cycle 1

Treatment medication table. Patient may receive Lenalidomide + Dexamethasone OR Pomalidomide + Dexamethasone.

Agent	Dose Level	Route	Day	ReRx
Lenalidomide	25 mg*	Oral	Cycle 1: Day 1-14	Cycle 1: 21 days
Pomalidomide	4 mg	Oral	Cycle 1: Day 1-21	Cycle 1: 21 days
Dexamethasone	40 mg**	Oral	Cycle 1: Day 1 ,8, ,15	Cycle 1: 21 days

Cycle 1 length = 21 days

* Starting dose will b determined as per the creatinine clearance below (see 7.12)

** The dose of dexamethasone used can be determined by the treating physician and omitted if needed.

Cohort A and B Cycles 2-6

Treatment Medication Table. Patient may receive Lenalidomide based regimens.

Agent	Dose Level	Route	Day	Re Rx
Lenalidomide	25 mg*	Oral	Cycle 2-6: Day 1-21	Cycles 2-6: 28 days
Dexamethasone	40 mg**	Oral	Cycle 2-6: Day 1 ,8, ,15. 22	Cycles 2-6: 28 days

Note: Standard of care agents can be added for cycles 2-6 as long as the regimen contains lenalidomide

Cycles 2-6 length = 28 days

* Any dose-adjustments will be determined as per the creatine clearance below (see 7.12).

** The dose of dexamethasone used can be determined by the treating physician and omitted if needed.

Cohort C and D Cycles 2-6

Treatment medication table. Patient may receive Lenalidomide based regimen OR Pomalidomide based regimen.

Agent	Dose Level	Route	Day	ReRx
Lenalidomide	25 mg*	Oral	Cycles 2-6: Day 1-21	Cycles 2-6: 28 days
Pomalidomide	4 mg	Oral	Cycles 2-6: Day 1-21	Cycles 2-6: 28 days
Dexamethasone	40 mg**	Oral	Cycle 2-6: Day 1 ,8, ,15, 22	Cycles 2-6: 28 days

Note: Standard of care agents can be added for cycles 2-6 as long as the regimen contains lenalidomide or pomalidomide

Cycles 2-6 length = 28 days

* Any dose-adjustments will be determined as per the creatinine clearance below (see 7.12).

** The dose of dexamethasone used can be determined by the treating physician and omitted if needed.

7.12

Creatinine Clearance (CrCl)	Lenalidomide Dose
CrCl >60 ml/minute	25 mg No adjustment required
CrCl 30-60 ml/minute	10 mg once daily (may increase to 15 mg once daily after 2 cycles if nonresponsive but tolerating treatment)
CrCl <30 ml/minute (non-dialysis dependent)	15 mg every 48 hours

7.2 Treatment by local medical doctor (LMD)

The registering investigator is responsible for all treatment decisions and for the collection and submission of the study data in accordance with the approved protocol. (**Note:** Treatment with local MD is allowed as long as the patient is able to come back to the registering site for sample collections under IRB # 521-93 or IRB# 14-009163).

When it has been determined that a patient's malignant disease is stable or objective tumor regression has been observed and the patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be sent with the patient for

administration by the patient's Local Medical Doctor (LMD). The registering physician retains responsibility for the patient.

In this case, a written statement outlining drug dosage, method of administration, follow-up tests required, and telephone number to call to discuss any questions with the registering investigator must be sent with the patient to provide necessary information to the LMD. The LMD will be required to supervise the administration of the study drugs as stipulated in the protocol and provide written documentation that the drug was administered.

The registering investigator is responsible for all treatment decisions and for the collection and submission of the study data in accordance with the approved protocol.

The responsible investigator will ensure the integrity of the local physician, facilitate drug accountability, and ensure that the LMD can rapidly communicate toxicity.

7.3 End of study

All patients in Cohort A, Cohort B, Cohort C and Cohort D enrolled on this clinical trial will be treated on this study only for 6 cycles from the time of registration. After this time, they will no longer be part of the study and will be taken off study but can continue on their current therapy or any other therapy as deemed appropriate by their physician.

Patients can then continue the therapy instituted beyond cycle 1 with any additional therapeutic agents as deemed appropriate by their physician and/or local physician.

8.0 Dosage Modification Based on Adverse Events

Any adverse event noted in the study and its resultant dose-modifications should be managed as per the prescribing information of lenalidomide, dexamethasone and/or pomalidomide as per which of these two drugs the adverse event is attributable to.

8.1 Lenalidomide Dose Modifications

Lenalidomide (Cycle 1: Day 1-14 Cycle 2-6: Day 1-21)	
Starting dose	25mg
-1	10 mg
-2	Discontinue

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Investigations	Platelet count decreased Grade 4	Lenalidomide	*Omit dose until AE has resolved to Grade 1 or better • Follow CBC weekly • If thrombocytopenia <30,000/mm^3 recurs, reduce dose by one dose level (by 5 mg) and continue therapy when platelet count ≥30,000/mm^3 If, after lenalidomide has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on remaining agent(s) till the completion of maintenance and then proceed to off study
	Neutrophil count decreased Grade 4		*Omit dose until AE has resolved to Grade 2 or better • Follow CBC weekly * If neutropenia has resolved to ≤Grade 2, resume dose at one level lower *If, after lenalidomide has been omitted, and the AE does not return to ≤Grade 2within 4 weeks, then the patient may continue on remaining agent(s) till the completion of maintenance and then proceed to off study
Blood and lymphatic system disorders	Anemia Grade 4		*Omit dose until AE has resolved to Grade 2 or better • Follow CBC weekly * If anemia has resolved to ≤Grade 2, resume dose at one level lower *If, after lenalidomide has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on remaining agent(s) till the completion of maintenance and then proceed to off study
	Febrile neutropenia ≥Grade 3		• Omit dose and follow CBC weekly • If neutropenia has resolved to ≤Grade 2, resume dose at same level with GCSF support (See Section 9.2

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Cardiac disorders	Sinus bradycardia/ other cardiac arrhythmia Grade 2	Lenalidomide	Omit dose and follow at least weekly until resolution • If AE resolves to ≤Grade 1, reduce dose by one dose level and continue therapy
	≥ Grade 3		• Discontinue study treatment and go off study
Vascular disorders	Thromboembolic event ≥ Grade 3		• Omit dose and start anticoagulation; restart at investigator's discretion (maintain dose level)
Immune system disorders	Allergic reaction Grade 2-3		• Omit dose and follow at least weekly until resolution • If AE resolves to ≤Grade 1, reduce dose level and continue therapy
	Anaphylaxis Grade 4		• Discontinue study treatment and go off study
Skin and subcutaneous tissue disorders	Erythema multiforme ≥Grade 3		Discontinue study treatment and go off study
	Skin ulceration ≥Grade 2		Discontinue study treatment and go off study
	Other: Non-blistering rash Grade 3		• If Grade 3 omit dose and follow weekly until resolution • If AE resolves to ≤Grade 2 continue therapy
	Other: Non-blistering rash Grade 4		• Discontinue study treatment and go off study
Other AEs	Non-hematologic AE assessed as related to lenalidomide ≥Grade 3		• Omit dose and follow at least weekly until resolution • If the AE resolves to ≤Grade 2, implement one dose reduction step and continue therapy (per Table 8.1)

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic applications.ctc.htm

** Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

8.2 Standard of Care Agents Dose Modifications (not lenalidomide)

8.21 Standard of care dose modifications will be adjusted as per standard of care guidelines in the prescribing information for multiple myeloma patients.

8.3 Dexamethasone–Related Treatment Modification Guidelines for Adverse Events

8.31 Dexamethasone Dose Modifications

Dose Level	**Dexamethasone (Cycle 1: Day 1, 8, 15) Cycle 2-6: Day 1, 8, 15, 22)** (Age <75)	**Dexamethasone (Cycle 1: Day 1, 8, 15) Cycle 2-6: Day 1, 8, 15, 22)** (Age ≥75)
Starting Dose	40 mg	20 mg
-1	20 mg	8 mg
-2	8 mg	Discontinue
-3	Discontinue	

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified ← ←

CTCAE SOC	Adverse event	Severity	Action on Dexamethasone
Gastrointestinal disorders	Dyspepsia, ulcer, or gastritis	Grade 1-2	Treat with histamine-H2 receptor blockers, sucralfate, or proton-pump inhibitors. If symptoms persist despite these measures, decrease by 1 dose level.
		≥Grade 3	Omit dexamethasone until symptoms adequately controlled. Restart and decrease 1 dose level of current dose along with concurrent therapy with histamine-H2 receptor blockers, sucralfate, or omeprazole. If symptoms persist despite these measures, discontinue and do not resume
	Pancreatitis	≥Grade 3	Permanently discontinue
General disorders and administration site conditions	Localized edema	≥Grade 2	Intervention indicated (eg, diuretics) as needed and decrease by 1 dose level. If edema persists despite these measures, decrease dose another level at investigator discretion. Discontinue and do not resume if symptoms persist despite 2nd reduction.
Psychiatric disorders	Confusion or Agitation	≥Grade 2	Omit dexamethasone until symptoms resolve. Restart with 1 dose level reduction. If symptoms persist despite these measures, permanently discontinue dexamethasone.
Musculoskeletal and connective tissue disorders	Generalized muscle weakness	≥Grade 2	Decrease dexamethasone dose by 1 dose level. If weakness persists despite these measures, decrease dose further by 1 dose level at investigator discretion. Permanently discontinue dexamethasone if symptoms persist.

CTCAE SOC	Adverse event	Severity	Action on Dexamethasone
Metabolism and nutrition disorders	Hyperglycemia	≥Grade 2	Treatment with insulin or oral hypoglycemia as needed. If uncontrolled despite these measures, decrease dose by 1 dose level until blood glucose levels are satisfactory

Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

8.4 Pomalidomide–Related Treatment Modification Guidelines for Adverse Events

8.41 Pomalidomide Dose Modifications

Dose Level	**Pomalidomide (Cycle 1: Day 1-21 Cycle 2-6: Day 1-21)**
Starting dose	4 mg
-1	3 mg
-2	2 mg
-3	1 mg
-4	Discontinue

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified ← ←

CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Investigations	Neutrophil count decreased If ANC $<1.0 \times 10^9$/L or ANC $>1.0 \times 10^9$/L (up to LLN) with fever (temperature >38.5°C)	Pomalidomide	Omit pomalidomide dose. Follow CBC weekly. If neutropenia has resolved to ≤Grade 2 prior to Day 21 and fever has resolved, restart pomalidomide at next lower dose level and continue through Day 21of a 28-day cycle. If febrile neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the pomalidomide dose maintained.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Investigations	Platelet count decreased If platelet count <30 × 10^9/L	Pomalidomide	Omit pomalidomide dose Follow CBC weekly Hold anticoagulation/antiplatelet therapy until platelets ≥50,000/mm³ If platelet count resolves to ≤Grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21 of each cycle
Skin and subcutaneous tissue disorders	Rash maculopapular Grade 2 or 3	Pomalidomide	Omit pomalidomide dose; follow weekly If the AE resolves to ≤Grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21of each cycle
	Grade 3-4 Stevens –Johnson Syndrome	Pomalidomide	Discontinue pomalidomide and remove patient from all study treatment
	≥Grade 3 Erythema multiforme	Pomalidomide	Discontinue pomalidomide and remove patient from all study treatment
	Erythroderma ≤Grade 3	Pomalidomide	Omit pomalidomide dose; follow weekly If the AE resolves to ≤Grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21of the 28-day cycle
	Rash, maculo-papular Rash, acneiform Grade 4	Pomalidomide	Discontinue pomalidomide and remove patient from all study treatment
Nervous system disorders	Peripheral sensory neuropathy Grade 3	Pomalidomide	Omit pomalidomide dose and follow at least weekly. If the AE resolves to ≤Grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21
	Peripheral sensory neuropathy Grade 4	Pomalidomide	Discontinue pomalidomide and remove patient from all study treatment

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Immune system disorders	Allergic reaction Grade 2-3	Pomalidomide	Omit dose and follow at least weekly If the AE resolves to ≤Grade 1 prior to Day 15, restart at next lower dose level and continue through Day 21
	Allergic reaction Grade 4	Pomalidomide	Discontinue pomalidomide and remove patient from all study treatment
Vascular disorders	Thromboembolic event ≥ Grade 3	Pomalidomide	Omit dose and start anticoagulation Restart at investigator's discretion (maintain dose level)
Endocrine disorders	Hyperthyroidism or Hypothyroidism ≥ Grade 2	Pomalidomide	Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy Reduce the dose of pomalidomide by 1 dose level.
Other non-hematologic adverse event	Other non-hematologic ≥Grade 3	Pomalidomide	If the AE can be attributed to either of the drugs, pomalidomide should be discontinued at first instance b for recurrence of the same toxicity necessitating dose modification Omit pomalidomide dose. Follow at least weekly If the toxicity resolves to ≤Grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

8.4 Standard of Care Agents Dose Modifications (not pomalidomide)

8.41 Standard of care dose modifications will be adjusted as per standard of care guidelines in the prescribing information for multiple myeloma patients.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 28, No 33 (November 20), 2010: pp. 4955-5010 (darbepoetin/epoetin).

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea

Diarrhea could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug

- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
Mayo Clinic Sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	**Mayo Sites – attach to MCCC Electronic SAE Reporting Form** http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56	Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form:http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to CANCERCROSAFETYIN@mayo.edu and RSTP2CSAES@mayo.edu

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0 A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 5.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.

Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm**

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch 3500A for Health Professionals (complete all three pages of the form).

  http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

10.32 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported via expedited mechanisms[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for Commercial or Commercial Imaging Agents (Non-IND) Agent(s) ONLY:

10.41 Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND trial within 30 Days of the Last Administration of a Commercial Agent[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 for investigational agents or commercial/investigational agents on the same arm.

For commercial agents (for commercial agent(s) on its own arm):

Attach the MedWatch 3500A form to the Mayo Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56.

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, 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
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56, to submit to CANCERCROSAFETYIN@mayo.edu. The Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) of General disorders and administration site conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)

- Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation. Include this form: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v5.0 **unless** alternate grading is indicated in the table below:

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Anemia	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Gastrointestinal Disorders	Nausea	X	X
	Diarrhea		X
	# of stools	X	
	Vomiting	X	X
General disorders and administration site conditions	Fatigue	X	X
Vascular disorders	Thromboembolic event	X	X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly

treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Treatment Evaluation/Measurement of Effect

The International Myeloma Working Group (IMWG) uniform response criteria(*23*) will be used to assess response to therapy.

11.1 Terms and definitions

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

  Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.
  - M-proteins migrating in the β-region (usually IgA M-proteins)
  - Cases in which the M-protein is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
  - Cases in which there are multiple peaks of same M-protein (aggregates or dimers)

  If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted, with the exception that quantitative IgG may not be used. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-protein values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

  Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

  FLC estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine M-protein.

  - Serum M-protein ≥0.5 g/dl

    NOTE: Quantitative IgG may not be used for defining measurable disease

  - Urine M-protein ≥ 200 mg/24 h
  - Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal
  - Bone marrow plasma cells ≥ 30%
  - Measurable bone or extramedullary disease on imaging.

Measurable disease			
Cohort A (Smoldering MM),	**Cohort B** (Newly Diagnosed MM)	**Cohort C** (Relapsed/Refractory MM)	**Cohort D** (Relapsed on Len maintenance)
Patients who have a measurable serum or urine M-protein. o Serum M-protein ≥0.5 g/dl NOTE: Quantitative IgG may not be used for defining measurable disease o Urine M-protein ≥ 200 mg/24 h o Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal o Bone marrow plasma cells	Patients who have a measurable serum or urine M-protein. o Serum M-protein ≥0.5 g/dl NOTE: Quantitative IgG may not be used for defining measurable disease o Urine M-protein ≥ 200 mg/24 h o Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal o Bone marrow plasma cells	Patients who have a measurable serum or urine M-protein. o Serum M-protein ≥0.5 g/dl NOTE: Quantitative IgG may not be used for defining measurable disease o Urine M-protein ≥ 200 mg/24 h o Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal o Bone marrow plasma cells	Patients who have a measurable serum or urine M-protein. o Serum M-protein ≥0.5 g/dl NOTE: Quantitative IgG may not be used for defining measurable disease o Urine M-protein ≥ 200 mg/24 h o Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal o Bone marrow plasma cells

≥ 30% o Measurable bone or extramedullary disease on imaging.	≥ 30% o Measurable bone or extramedullary disease on imaging.	≥ 30% o Measurable bone or extramedullary disease on imaging.	≥ 30% o Measurable bone or extramedullary disease on imaging.

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. ***Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine M-protein) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results*** with the exception of defining stringent complete response.

- **Evaluable disease**: Patients who do not have a "measurable" serum M-protein, serum free light chain, or urine M-protein.

- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-protein or urine M-protein, but has had a detectable M-protein in his/her serum and/or urine and/or measurable serum free light chain.

- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable M-protein in his/her serum and/or urine.

11.2 Confirmed response

In order to be classified as a hematologic response, confirmation of serum M- protein, serum immunoglobulin free light chain (when primary determinant of response) and urine M- protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case.

- Radiographic studies are not required to satisfy these response requirements; however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

11.3 Bone progression

Caution must be exercised to avoid rating progression on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from the study.

11.4 Response and Progression

Criteria for response and progression are listed in Table 11.5. Progressive disease for all patients as defined in Table 11.5.

Table 11.5	
STANDARD IMWG RESPONSE CATEGORY	**RESPONSE CRITERIA [a]**
Stringent Complete Response (sCR) [b]	CR as defined *plus* Normal FLC ratio *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4- color flow cytometry [i]
Complete Response (CR) [b]	• Negative immunofixation of serum and urine [c] *and* • Disappearance of any soft tissue plasmacytoma *and* • <5% PCs in Bone Marrow *and* • If the only measurable disease is FLC, a normal FLC ratio [d] • For patients with extramedullary plasmacytoma present at baseline: a) FDG-avid or PET positive prior to therapy: Mass of any size permitted if PET negative and b) Variably FDG-avid or PET negative: Regression to normal size on CT. For patients with only skin involvement, these same criteria apply to skin lesions measured with a ruler.
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis [c] *or* • ≥90% reduction in serum M-protein and urine M-protein <100 mg/24 h [c] • If the only measurable disease is FLC, a >90% reduction in the difference between involved and uninvolved FLC levels • Not applicable for those patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike at baseline
Partial Response (PR)	• If present at baseline, ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24hrs [c] • If the only measurable disease is FLC, a ≥50% reduction in the difference between involved and uninvolved FLC levels • If the only measurable disease is BM, a ≥ 50% reduction in BM PCs (provided the baseline PCs was ≥ 30%)

	• If present at baseline, ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas [j] • For patients with extramedullary plasmacytoma present at baseline: ≥50% decrease in SPD of up to 6 largest dominant masses and a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved sites OR b) Variably FDG-avid or PET negative: regression on CT or by measurements with a ruler in patients with only skin involvement
Minimal Response (MR)	• If present at baseline, ≥25% but ≤ 49% reduction of serum M protein *and* reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours [c] *and* • If present at baseline, ≥25% reduction in the size (SPD) of soft tissue plasmacytoma [j]
Stable Disease (SD)	• Not meeting criteria for sCR, CR, VGPR, PR, MR or PD
Progressive Disease (PD) [b, h]	Increase of 25% from lowest value in any of the following [f, g]: • Serum M-protein (absolute increase must be ≥ 0.5 g/dL) *and/or* • Urine M-protein (absolute increase must be ≥ 200 mg/24 hrs) *and/or* • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) *and/or* • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be ≥ 10%) [e] • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of more than one lesion, or ≥50% increase in longest diameter of a previous lesion >1 cm in short axis. Lesions PET positive if PET positive prior to therapy Or any one or more of the following: • Development of new bone lesion or soft tissue plasmacytoma or ≥50% increase from nadir in the size (SPD) of existing bone lesions or soft tissue plasmacytoma or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis [j] • 50% increase in circulating plasma cells (minimum of 200 cells per L) if this is the only measure of disease

Clinical Relapse	One or more of the following direct indicators of increasing disease and/or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder: 1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dL; >2.875mM/L) 4. Decrease in hemoglobin of more than 2 g/dL (1.25mM) or to less than 10 g/dL 5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177mM/L) 6. Hyperviscosity

[a] All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at any time before the institution of any new therapy. sCR, CR, VGPR, PR, MR and SD categories require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u"] to designate first time point at which response category MAY have been achieved if confirmed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

[b] CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient.

[c] If more than one M protein spike meets the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

[d] In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.

[e] Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC;

[f] A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum M-protein is ≥ 5 g/dL, an increase in serum M-protein of ≥ 1 g/dL is sufficient to define disease progression.

[g] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

[h] Progressive disease should be confirmed on two consecutive evaluations, where the timing of confirmation is per the treating physician and can be done immediately within the same cycle or on the next cycle. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

[i] Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

[j] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the sum of the products of the maximal perpendicular diameters of measured lesions (SPD).

12.0 Descriptive Factors

12.1 Prior treatment: 0 vs 1 vs 2 vs 3+

12.2 Parameters followed for hematologic response: serum monoclonal protein ≥0.5 g/dL and urine monoclonal protein ≥200 mg/24 hours vs. serum monoclonal protein ≥0.5 g/dL only vs. urine monoclonal protein ≥200 mg/24 hours only vs. serum immunoglobulin free light chain ≥10 mg/dL vs. bone marrow plasma cells >= 30% vs. measurable bone or extramedullary disease on imaging. Distinguish between SPEP measurements versus quantitative IgA measurements versus quantitative IgD measurements for serum monoclonal protein.

12.3 mSMART FISH risk level: high risk vs low risk vs unknown.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Off protocol treatment

Patients who go off protocol treatment before completing 6 cycles of treatment will not continue to be followed.

13.2 Criteria for Treatment Discontinuation
Patients may discontinue treatment for the following reasons:
• Progressive multiple myeloma (see Section 11.0)
• Patient withdraws consent to continue in the trial
• Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
• The Investigator withdraws the patient in the patient's best interests
• Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions)
• Administrative reasons (e.g., the patient is transferred to hospice care)
• An adverse event, which in the opinion of the investigator precludes further trial participation

Patients will be taken off study if they discontinue treatments for any of the reasons above.

13.3 Criteria for Study Discontinuation
The study may be temporarily or permanently discontinued at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:
• Safety concerns
• Non-compliance with the protocol, Good Clinical Practice guidance or other regulatory requirements by the Investigator(s)
• Request to discontinue the trial by a regulatory or health authority or an IRB

134 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted. No further data submission is necessary.

13.5 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

13.6 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Protocol Treatment/Intervention Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Note: Biospecimen Collection will be done under separately established IRB # 521-93 or IRB# 14-009163 or 919-04

Research	Specimen Purpose (check all that apply)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Prior to D1C1	Prior to D1C2	End of treatment (optional)	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Bone marrow plasma	☒ Correlative ☐ Eligibility Confirmation ☐ Banking ☐ Other	Mandatory	Bone marrow aspirate	EDTA (purple)	4 mL (1)	X	X	X	Yes	Cool Pack or Ice
Bone marrow cells	☒ Correlative ☐ Eligibility Confirmation ☐ Banking ☐ Other	Mandatory	Bone marrow aspirate	ACD (yellow)	35 mL (1)	X	X	X	Yes	Cool Pack or Ice
Peripheral Blood	☒ Correlative ☐ Eligibility Confirmation ☐ Banking ☐ Other	Mandatory	Whole Blood	ACD (yellow)	18 mL (1)	X	X	X	Yes	Cool Pack or Ice

14.2 Shipping and Handling

Kits will not be used. Each site will use their own supply of tubes

14.22 Shipping

Bone marrow and blood samples can be shipped with Cool Pak the same day they are collected (Monday-Thursday). They should be shipped priority overnight taking care to avoid Friday collection and shipping. If unavoidable, Friday shipping with Saturday delivery can be arranged contacting the laboratory **in advance**.

Please notify Mayo Clinic by email lehman.stacey@mayo.edu or phone (507) 284-3805 to notify laboratory when specimens are being shipped.

Stacey Lehman
Mayo Foundation
221 4th Avenue SW
Stabile 613
Rochester, MN 55905

14.3 Metabolomics profiling

To determine if specific metabolite profiles within the bone marrow and peripheral blood plasma will be reflective of the metabolic phenotype within the clonal bone marrow plasma cells that predict for response to therapy with an IMiD.

Methodology: For this analysis, bone marrow and peripheral blood plasma will undergo large scale, untargeted metabolite profiling via liquid chromatography mass spectrometry. Differentially expressed metabolites in responder versus non-responders will be evaluated for the development of a potential biomarker predicting clinical response.

Sample type and timing: Bone marrow aspirate samples will be collected in (1) 5 ml EDTA (purple top) tube and placed on ice or a cool pack. Samples to be collected prior to cycle 1 and then prior to cycle 2.

Sample Destination:

Stacey Lehman
Mayo Foundation
221 4th Ave SW 613 Stabile
Rochester, MN 55905

14.4 Multiple myeloma cell retrieval

Samples type and timing: For studies utilizing intracellular metabolomics as well as genomics and transcriptomics of the MM cells, 35 ml of bone marrow aspirate will be obtained in (6) 6 mL ACD (yellow top) tubes in addition to the 5

ml of bone marrow aspirate from the (1) 5 mL EDTA (purple top) tube prior to cycle 1 and then prior to cycle 2.

Sample Destination:

Stacey Lehman
Mayo Foundation
221 4th Ave SW 613 Stabile
Rochester, MN 55905

15.0 Drug Information

IND exempt (159997)

15.1 Lenalidomide for Oral Administration (Revlimid®)

15.11 **Background**: Lenalidomide has antineoplastic, immunomodulatory and antiangiogenic characteristics via multiple mechanisms. Lenalidomide selectively inhibits secretion of proinflammatory cytokines (potent inhibitor of tumor necrosis factor-alpha secretion); enhances cell-mediated immunity by stimulating proliferation of anti-CD3 stimulated T cells (resulting in increased IL-2 and interferon gamma secretion); inhibits trophic signals to angiogenic factors in cells. Lenalidomide inhibits the growth of myeloma cells by inducing cell cycle arrest and cell death.

15.12 **Formulation and Dispensing**: Commercially available for oral administration as: Capsules: 5 mg, 10 mg, 15 mg and 25 mg

Lenalidomide is approved for marketing only under a FDA approved, restricted distribution program called RevAssist. Physicians, pharmacies, and patients must be registered; a maximum 28-day supply may be dispensed; a new prescription is required each time it is filled; pregnancy testing is required for females of childbearing potential.

15.13 **Preparation, storage, and stability**: Store oral capsules at controlled room temperature between 15ºC and 30ºC (59 ºF and 86 ºF). Refer to labeling on the bottle for expiration date of the commercial tablets.

15.14 **Administration:** Refer to the treatment section for specific administration instructions. Administer with water. Swallow capsule whole; do not break, open, or chew.

15.15 **Pharmacokinetic information**:
Absorption: Rapid
Metabolism: Approximately two-thirds of Lenalidomide is eliminated unchanged through urinary excretion.
Protein binding: ~30%
Time to peak, plasma: Healthy volunteers: 0.6-1.5 hours; Myeloma patients: 0.5-4 hours
Half-life elimination: ~3 hours
Excretion: Urine (~67% as unchanged drug)

15.16 **Potential Drug Interactions**:
Increased Effect/Toxicity: Abatacept and Anakinra may increase the risk of serious infection when used in combination with Lenalidomide. Lenalidomide may increase the risk of infections associated with vaccines (live organism).
Decreased Effect: Lenalidomide may decrease the effect of vaccines (dead organisms).
Herb/Nutraceutical Interactions: Avoid echinacea (has immunostimulant properties; consider therapy modifications).

15.17 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Boxed Warnings:
1. Potential for human birth defects
2. Hematologic toxicity (neutropenia and thrombocytopenia)
3. Deep Venous Thrombosis and Pulmonary Embolism

Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema
Central nervous system: Fatigue, pyrexia, dizziness, headache
Dermatologic: Pruritus, rash, dry skin
Endocrine & metabolic: Hyperglycemia, hypokalemia
Gastrointestinal: Diarrhea, constipation, nausea, weight loss, dyspepsia, anorexia, taste perversion, abdominal pain
Genitourinary: Urinary tract infection
Hematologic: Thrombocytopenia, neutropenia, anemia, myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction
Infection, especially when white blood cell count is low
Neuromuscular & skeletal: Muscle cramp, arthralgia, back pain, tremor, weakness, paresthesia, limb pain, muscle spasms
Ocular: Blurred vision
Respiratory: Nasopharyngitis, cough, dyspnea, pharyngitis, epistaxis, upper respiratory infection, pneumonia, shortness of breath

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Edema, deep vein thrombosis, hypertension, chest pain, palpitation, atrial fibrillation, syncope
Central nervous system: Insomnia, hypoesthesia, pain, depression
Dermatologic: Bruising, cellulitis, erythema
Endocrine & metabolic: Hypothyroidism, hypomagnesemia, hypocalcemia
Gastrointestinal: Vomiting, xerostomia, loose stools
Genitourinary: Dysuria
Hematologic: Leukopenia, febrile neutropenia, Lymphopenia
Hepatic: ALT increased, abnormal hepatic function tests
Neuromuscular & skeletal: Myalgia, rigors, neuropathy
Respiratory: Sinusitis, rhinitis, bronchitis, pulmonary embolism
Miscellaneous: Night sweats, diaphoresis, fever

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Angioedema, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, Tumor Lysis Syndrome, Graft vs. Host Disease, rhabdomyolysis, Kidney damage which may require dialysis

15.18 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

As a requirement of the REMS program, access to Lenalidomide is restricted. Lenalidomide is approved for marketing only under a FDA approved, restricted distribution program called REVLIMID REMS (www.REVLIMIDREMS.com) formerly known as the RevAssist program. Physicians, pharmacies, and patients must be registered; a maximum 28-day supply may be dispensed; a new prescription is required each time it is filled; pregnancy testing is required for females of childbearing potential.

15.19- Nursing Guidelines-Lenalidomide

15.191 Myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction. Monitor CBC w/diff regularly. Instruct patient to report any unusual bruising or bleeding (thrombocytopenia); signs and symptoms of infection (neutropenia); and energy conserving lifestyle (anemia).

15.192 Lenalidomide can have thrombotic adverse events (i.e DVT and PE). Instruct patient to report any limb swelling or pain, and to seek medical attention for shortness of breath or chest pain.

15.193 Because of the potential for birth defects patients should be instructed in effective methods of birth control. Female patients should use 2 forms of birth control during treatment and for 4 weeks after discontinuing therapy. Males must be instructed to use a latex condom during any sexual contact with a woman of child bearing potential (even if they have had a vasectomy), because it is unknown if lenalidomide is present in semen.

15.194 Patents may experience pruritus, rash and dry skin. Because of the rare risk of Steven's Johnson Syndrome, patients should immediately report any rash to their provider.

15.195 Drug may cause hyperglycemia. Patients with diabetes or impaired fasting glucose may need to have their glucose levels monitored more closely.

15.196 Gastrointestinal side effects (diarrhea, constipation, nausea, dyspepsia, anorexia, etc) are commonly seen. Manage patent symptomatically and monitor for effectiveness.

15.197 Patients may experience myalgias, arthralgias, parasthesias and other generalized pain. Administer analgesics as ordered and monitor for their effectiveness. Rarely infective bursitis and arthritis have been reported. Instruct patients to report any joint pain or redness to study team immediately.

15.198 Upper respiratory symptoms (nasopharyngitis, cough, epistaxis, etc.) can be seen. Manage symptomatically and monitor for effectiveness.

15.199 Agent may cause fatigue, dizziness, vertigo or blurred vision. Instruct patients to use caution when driving or operating machines.

15.200 Monitor LFT's and report any elevations to the study team. Instruct patient to report abdominal pain and/or jaundice to the study team.

15.201 All prescribers and patients must be enrolled into the REVLIMID REMS program. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

15.202 Rarely secondary malignancies have been seen after lenolidamide therapy, including MDS, squamous/basal cell carcinomas of the skin, T-cell type acute leukemia.
15.203 Monitor Renal function, renal failure has been reported.
15.204 Acute GVHD following Allo Transplant has been seen.
15.205 Rarely tumor lysis syndrome has been seen. Monitor appropriate TLS labs and report any abnormalities to the study team.

15.2 Pomalidomide (CC-4047, Pomalyst®)

15.21 **Background**: Pomalidomide (CC-4047) is a novel drug in the class of immunomodulatory agents known as IMiDs compounds. Pomalidomide binds to its molecular target cereblon (CRBN), a protein that is part of an E3 ubiquitin ligase complex, which is responsible for the polyubiquitination of substrate proteins, targeting them for subcellular redistribution and destruction by the proteasome. The pharmacologic properties of pomalidomide are of potential therapeutic benefit in the treatment of various hematologic neoplasms (such as multiple myeloma and myeloproliferative neoplasm-associated myelofibrosis), non-neoplastic hematologic disorders (such as β-thalassemia and sickle cell disease) and non-hematologic disorders such as systemic sclerosis, as well as solid tumor neoplasms.

15.22 **Formulation**: Pomalidomide capsules can be 0.5-mg gelatin capsules (size 4 reddish brown), 1-mg hard gelatin capsules (size 4 reddish brown), 2-mg (size 2 reddish-brown), 3-mg and 4-mg hard gelatin capsules (size 2 reddish-brown), and 5-mg hard gelatin capsules (size 1 reddish-brown), containing pomalidomide, mannitol, pregelatinized starch, and sodium stearyl fumarate.

Pomalidomide capsules are supplied in high density polyethylene (HDPE) containers fitted with induction seals and child-resistant plastic closures or PVC/PCTFE blister with push-through foil.

15.23 **Preparation and storage**: Store drug at controlled room temperature, between 68-77 ºF (20-25ºC) or as indicated on the manufacturer's label. The expiration date is indicated on the label.

Only enough study drug for one month of therapy may be dispensed.

15.24 **Administration:** Pomalidomide is administered by mouth at approximately the same time each day. Capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment. Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

15.25 **Pharmacokinetic information**:
a) Absorption – oral absorption has been moderately rapid with first dose C_{max} occurring in 1.5 to 4 hrs. More than 70% of the pomalidomide dose is absorbed

in humans. A high fat meal decreased the rate of absorption but had minimal effect on overall extent of absorption; therefore drug may be administered without regard to food intake.
b) Distribution – Apparent volume of distribution in healthy subjects ranged from 74-138 L across a dose range of 1 to 10 mg daily. Pomalidomide protein binding in human plasma is low to moderate (15.8% for R-enantiomer, 42.2% for S-enantiomer) and the binding is concentration independent in the concentration range of 30 and 1000 ng/mL. Drug distributes into semen.
c) Metabolism – Eight metabolites were detected in plasma, each at exposures < 10% of the plasma pomalidomide. CYP-dependent metabolites accounted for approximately 43% of the excreted radioactivity, while non-CYP dependent hydrolytic metabolites accounted for 25%, and excretion of unchanged pomalidomide accounted for 10%.
d) Excretion – In healthy patients, 72.8% of the dose was recovered in urine and 15.5% was recovered in feces. Less than 3% of the dose is excreted as unchanged pomalidomide in the urine. The geometric mean terminal elimination half-life ($t_{1/2}$) of pomalidomide was approximately 7.5 hours.

In pomalidomide renal studies, no dose adjustment was required for subjects with renal impairment. On hemodialysis days, subjects were instructed to take pomalidomide following hemodialysis. No dose adjustment of pomalidomide is required for patients with hepatic impairment as defined by the Child-Pugh criteria.

15.26 **Potential Drug Interactions**: Pomalidomide is partially metabolized by CYP1A2 and CYP3A4/5. Pomalidomide is also a substrate for P-glycoprotein (P-gp). Coadministration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Coadministration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide increased mean exposure to pomalidomide by 125% compared to pomalidomide alone. If strong inhibitors of CYP1A2 are coadministered with pomalidomide, the pomalidomide dose by should be reduced 50%.
Smoking: Administration of pomalidomide in smokers, with smoking tobacco known to induce the CYP1A2 isoform, had no clinically relevant effect on exposure to pomalidomide relative to that exposure to pomalidomide observed in non-smokers.
Dexamethasone: Co-administration of multiple doses of 4 mg pomalidomide with 20 mg to 40 mg dexamethasone (a weak inducer of CYP3A) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone.

15.27 **Known potential toxicities**:
Very common known potential toxicities, ≥ 10%:
Anemia, leukopenia, neutropenia, thrombocytopenia, constipation, diarrhea, nausea, fatigue, peripheral edema, pyrexia, bronchitis, pneumonia, upper respiratory tract infection, decreased appetite, bone pain, muscle spasm, dizziness, peripheral neuropathy, blood creatinine increased, acute renal failure,

cough, dyspnea, pruritis

Common known potential toxicities, ≥1% - <10%:
Febrile neutropenia, pancytopenia, vertigo, vomiting, gastrointestinal hemorrhage, hemorrhoidal hemorrhage, rectal hemorrhage, hematochezia, gingival bleeding, bronchopneumonia, herpes zoster, nasopharyngitis, neutropenic sepsis, respiratory tract infection, alanine aminotransferase increased, increased liver function test, aspartate aminotransferase increased, gamma-glutamyltransferase increased, neutrophil count decreased, platelet count decreased, white blood cell count decreased, hyperkalemia, hyponatremia, depressed level of consciousness, peripheral sensory neuropathy, paresthesia, gait disturbance, polyneuropathy, hypoesthesia, neuralgia, peripheral motor neuropathy, tremor, confusional state, renal failure, renal impairment, hypercreatininemia, urinary retention, pelvic pain, pulmonary embolism, pruritus generalized, rash, swelling face, face edema, deep vein thrombosis

Uncommon and rare known potential toxicities, <1%:
Melena, Mallory-Weiss syndrome, upper gastrointestinal hemorrhage, mucosal hemorrhage, hyperbilirubinemia, blood bilirubin increased, transaminases increased, blood alkaline phosphates increased, liver function test abnormal, basil cell carcinoma, dysesthesia, areflexia, motor dysfunction, sensory disturbance, burning sensation, muscle atrophy, blood urea increased, creatinine renal clearance decreased, oliguria, glomerular filtration rate decreased, renal tubular necrosis, acute prerenal failure, azotemia, pneumonitis, interstitial lung disease, pruritis generalized, angioedema, urticarial, eyelid edema,

Frequency not defined:
Hepatitis, hepatitis B viral reactivation, tumor lysis syndrome, squamous cell carcinoma of skin, eye swelling, periorbital edema, lip swelling, swollen tongue, mouth edema, pharyngeal edema, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)

All study participants must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program. Females of reproductive potential must adhere to the scheduled pregnancy testing. Females of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves.

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

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

15.29 Nursing Guidelines

15.259 Agent is known to be teratogenic in rabbits. Therefore all women who are pregnant or who could become pregnant, should not handle the agent

outside of the original packaging. Chemotherapy gloves should be worn if contact is necessary.

15.260 Because of the similarity of this agent to thalidomide certain precautions MUST be employed by all subjects on protocol and for 4 weeks after discontinuation of agent. Instruct patients the following must be adhered to: No donation of tissue/blood/semen/sperm; sexually active males/ females must use protocol-specific contraception (regardless of fertility status-i.e. history of vasectomy).

15.261 Cytopenias are common (neutropenia most common). Monitor CBC closely and instruct patient to report any signs/symptoms of infection or unusual bruising or bleeding to the study team.

15.262 Thrombotic events have been reported. Anticoagulation prophylaxis may be recommended. Instruct patients to report any problems with bleeding, extremity pain or swelling, or shortness of breath to the study team immediately.

15.263 Patients may experience cough, URI, pneumonia, or sinusitis. Instruct patients to report respiratory symptoms to the study team.

15.264 Gastrointestinal side effects consisting of diarrhea, constipation, stomatitis, nausea, decreased appetite, and abdominal pain have been seen. Treat symptomatically and monitor for effectiveness.

15.265 Drug should be taken without food (at least 2 hours before or 2 hours after a meal). Do not open or crush capsules.

15.266 Patients may experience myalgias and muscle spasms. Treat symptomatically and monitor for effectiveness.

15.267 Fatigue is common. Instruct patient in energy conserving lifestyle.

5.199b Warn patients about the possibility of peripheral neuropathy, headache, confusion, and dizziness.

15.199c Patients may experience URI, pneumonia, dyspnea, and cough. Instruct patients to report respiratory symptoms to the study team.

15.199d Severe dermatologic reactions have been seen (including urticaria). Instruct patient to report and rash or skin changes to the study team.

15.199e All patients must be registered in the POMALYST REMS program. See protocol for more details.

15.99f Monitor creatinine, as patients may experience elevated creatinine levels, with rare reports of renal failure.

15.199g Rare reports of GI bleeding have been seen. Instruct patient to report any hematochezia, or melena to the study team immediately.

15.3 Dexamethasone for Oral Administration (DXM)

15.31 **Background**: Dexamethasone is an adrenal corticosteroid compound. Dexamethasone decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

15.32 **Formulation**: Commercially available for oral administration as:
Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg
Solution, oral: 0.5 mg/5 mL (500 mL)
Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL)

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20ºC to 25ºC (60ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF. Store oral liquid at room temperature, do not freeze. Do not use if solution contains a precipitate. Refer to commercial package for drug expiration date.

15.34 **Administration:** Refer to the treatment section for specific administration instructions. May be taken with meals to decrease GI upset.

15.35 **Pharmacokinetic information**:
Onset of action: Prompt
Duration of metabolic effect: 72 hours
Metabolism: Hepatic
Half-life elimination: Normal renal function: 4 ± 0.9 hours; **Biological half-life:** 36-54 hours
Time to peak, serum: Oral: 1-2 hours
Excretion: Urine (~10%)

15.36 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CYP3A4 (major), P-glycoprotein/ABCB1; **Induces** CYP2A6 (weak/moderate), 2C9 (weak/moderate), 3A4 (weak), UGT1A1
Increased Effect/Toxicity: Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.
Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids, separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone. Serum concentrations of isoniazid

may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.
Ethanol/Nutrition/Herb Interactions:
Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).
Food: Dexamethasone interferes with calcium absorption. Limit caffeine.
Herb/Nutraceutical: Avoid cat's claw, Echinacea (have immunostimulant properties)

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, frequency not defined:
Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 Nursing Implications:

15.391 Monitor regularly for hypertension, CHF and other evidence of fluid retention.

15.392 Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.

15.393 Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.

15.394 Evaluate signs of infection, particularly local candidal infections and treat appropriately.

15.395 Monitor blood glucose frequently.

15.396 Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.

15.397 Advise patient that easy bruising is a side effect.

16.0 Statistical Considerations and Methodology

16.1 Overview:

This is a pilot study to determine the response rates (>PR) of the combination of an immunomodulator and dexamethasone in Multiple Myeloma (MM) patients of each clinically relevant biomarker. This combination will be evaluated in four cohorts: Cohort A (Smoldering MM), Cohort B (Newly Diagnosed MM), Cohort C (Relapsed/Refractory MM) and Cohort D (Relapsed on Len maintenance). This study will not utilize a formal statistical design but will focus more on estimation rather than hypothesis testing.

16.11 Primary Endpoint: The primary endpoint of this trial is to estimate (>PR) response rates (RR) after one cycle of treatment. Biomarkers of interest will be identified and categorized into clinically relevant groups (e.g. positive vs. negative) by evaluating baseline and post treatment (after cycle one) biospecimens. RR will be estimated within each biomarker.

16.2 Statistical Design

Due to the lack of data to identify relevant biomarkers, the estimation of RR would be of interest. In each group, the response rates will be examined to see if there's any preliminary evidence to suggest further studies. This study will not utilize a formal statistical design.

For each biomarker category, the RR will be estimated by the number of patients who achieve a PR or better divided by the total number of evaluable patients in each cohort. Exact binomial 95% confidence intervals for these rates will be calculated.

16.22 Sample Size: A maximum of 30 evaluable patients will be accrued in cohort A and B and 60 patients in cohort C and D respectively. We anticipate accruing an additional 2 in cohort A and B and 3 in cohort C and D to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the maximum projected accrual is 190 patients (A: 32, B: 32, C: 63 and D: 63).

16.23 Accrual Rate and Study Duration: The anticipated accrual rate is 6 evaluable patients per month. Therefore, the accrual period for this pilot study is expected to be approximately 32 months. The final analysis can begin approximately 35 months after the trial begins, i.e. as soon as the last patient has been observed for 1 months and allowing 2 months for data entry.

16.24 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.3 Analysis Plan.

The analysis for this study is planned to start after data maturity has occurred. It is anticipated that the earliest date in which the result will be available via manuscript, abstract or presentation after the last registered patient has been followed for at least 1 month.

16.31 Primary Outcome Analyses:

Each cohort (A-D) will be evaluated separately and independently.

16.311 Definition:
The primary endpoint of this study is RR after 1 cycle of treatment. RR is defined as a binary variable. A success will be defined as patient who achieve a response of a PR or better using the IMWG criteria (Section 11.0) after one cycle of treatment. All patients meeting eligibility criteria who have signed a consent form, who complete at least one cycle of treatment and have successfully submitted biospecimens (pre and post treatment) will be evaluable for the endpoint.

Estimation: For each biomarker of interest, RR will be calculated by the number of successes divided by the total number of evaluable patients in each cohort.

16.32 Secondary Outcome Analyses

16.321 Biomarkers and RR will be analyzed using logistic regressions to identify predictive biomarkers.

16.322 RR among African American (AA) patients and white MM patients will be evaluated after one cycle of treatment. Chi-Square (or Fischer Exact) test and 95% confidence intervals will be estimated to compared AA and white patients descriptively.

16.323 Correlation between the depth of hematological responses and biomarkers will be estimated. Logistic regressions and chi square (or Fischer exact) testing will be utilized.

16.33 Data & Safety Monitoring:

The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

Adverse Event Stopping Rules: (Each cohort will be analyzed separately) The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse

event with attribute specified as “possible”, “probable”, or “definite”) that satisfy either of the following:

• If 3 or more out of the first 10 treated patients experience grade 4+ non-hematological toxicities
• If after the first 10 patients have been treated, 30% of patients experience grade 4+ non-hematologic toxicities

We note that we will review grade 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.4 Inclusion of Women and Minorities

16.41 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.42 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.43 Based on prior studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race. However, we are aiming to increase these percentages and accrue 15% of African American patientsto meet our secondary endpoints. If efforts to accrue in this racial category are not fruitful, the study will continue to accrue patients in the other racial categories. . Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	6	0	6
Not Hispanic or Latino	64	120	0	184
Unknown	0	0	0	0
Ethnic Category: Total of all subjects	64	125	0	**190**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	9	20	0	29
Native Hawaiian or other Pacific Islander	0	0	0	00
White	56	105	0	161
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects	64	125	0	**190**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa.

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens NA

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

N/A. See Section 4.

18.3 CRF completion

This study will use Medidata Rave for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for ensuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for diagnosis for all cohorts and relapse prior to study entry for Cohort C and Cohort D. These documents should be submitted within 14 days of registration.

Supporting documentation for diagnosis will include either a pathology report or a laboratory report demonstrating multiple myeloma (including SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and Aspirate, skeletal bone survey, PET scan, Plasma Cell Proliferation and Assessment and FISH). These reports should be uploaded into the Supporting Documentation: Baseline form within 14 days of registration.

For relapse of disease prior to study entry, supporting documentation includes the evidence needed to determine the patient's relapse prior to enrollment. These documents should be uploaded into the Supporting Documentation: Baseline form within 14 days of registration.

For response to treatment, supporting documentation may include SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and aspirate, skeletal bone survey, and PET scan. These documents should be uploaded into the Supporting Documentation form.

For patients who progress after study therapy supporting documentation may include any of the following: SPEP, UPEP, FLC, serum and urine immunofixation, bone marrow biopsy and aspirate, skeletal bone survey, and PET scan. These documents should be uploaded into the Supporting Documentation form.

18.6 Labeling of materials

Each site will be responsible for ensuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report will be distributed monthly by the data manager.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: Research testing on blood and tissue specimens. Bone marrow aspirate done at the end of Cycle 1 (prior to cycle 2) will be paid for by research.

19.3 Other budget concerns: Private benefactor funds through the Department of Development will provide Mayo Clinic with funding to support the costs of running this study.

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Appendix I ECOG Performance Status

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

*As published in Am. J. Clin. Oncol.:
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From http://www.ecog.org/general/perf_stat.html