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Phase II Trial of Sequential Treatment of Multiple Myeloma with Antibody Therapy

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Mayo Clinic Cancer Center

Phase II Trial of Sequential Treatment of Multiple Myeloma with Antibody Therapy

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√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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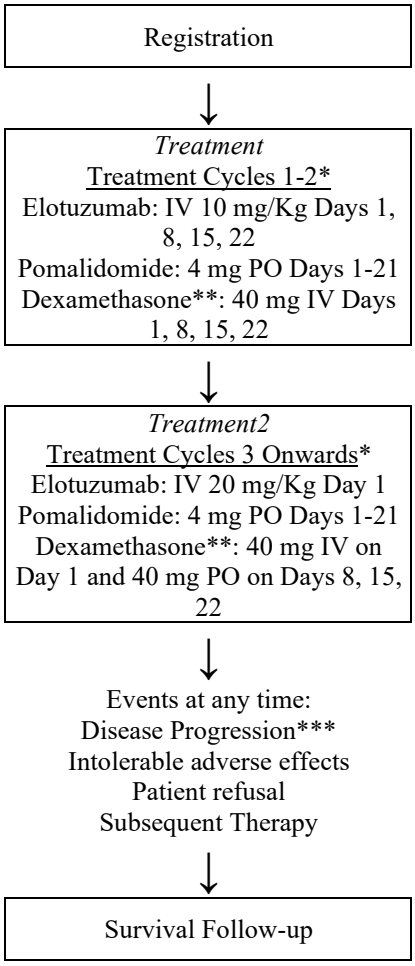
Schema



*Every Cycle = 28 days

****If patient age ≥75 years***, dexamethasone dosing will be 20 mg with same administration as shown in the schema

*****Confirmation of PD is not required. 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.

Generic name: Elotuzumab Brand name(s): Empliciti® Mayo Abbreviation: ELOTUZUMAB Availability: Commercial	Generic name: Pomalidomide Brand name(s): Pomalyst® Mayo Abbreviation: POMALIDOMIDE Availability: Commercial	Generic name: Dexamethasone Brand name (s): Decadron® Mayo Abbreviation: DXM Availability: Commercial

1.0 Background

Multiple myeloma (MM) is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The disease leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcemia), anemia, renal failure, neurological complications and hyper viscosity syndrome.

The majority of patients with MM produce a monoclonal protein, also called paraprotein, M-protein or M-component, which is an immunoglobulin (Ig) or a fragment of one that has lost its function.(Kyle & Rajkumar, 2009; Palumbo et al., 2009,) Normal immunoglobulin levels are compromised, leading to susceptibility of infections. The proliferating MM cells displace the normal bone marrow leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, which is reflected by clinical findings such as anemia, paraprotein in serum or urine, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs.(Kyle et al., 2003) Furthermore, hypercalcemia, renal insufficiency or failure, and neurological complications are frequently seen.(Palumbo & Anderson, 2011) A small minority of patients with MM are non-secretory.

At the time of diagnosis, multiple myeloma is a heterogeneous disease, with a course that varies on the basis of both disease- and host-related factors (e.g., age, renal function, stage, chromosomal abnormalities). Multiple myeloma causes significant morbidity and mortality. It accounts for approximately 1% of all malignancies and 13% of hematologic cancers. Approximately 50,000 patients per year are diagnosed with multiple myeloma in the EU and US, and 30,000 patients per year die due to multiple myeloma.

1.1 Treatment

1.11 Treatment choices for MM vary with age, performance status, comorbidity, the aggressiveness of the disease, and related prognostic factors.(Dingli et al., 2017) Despite great improvements in response rates and outcomes, nearly all patients have disease relapse and remain incurable. Furthermore, while several drugs and regimens are available for the treatment of MM, there are still questions regarding how the various regimens need to be sequenced.(Dingli et al., 2017) This becomes even more important as more complex combination regimens are being used earlier on in the treatment, making it necessary to utlize the available agents optimally for patients with relapsed/refractory MM (RRMM).

1.12 Role of Monoclonal Antibodies in Multiple Myeloma

So far two monoclonal antibodies are approved by the FDA for treatment of patients with RRMM – Daratumumab and Elotuzumab.(Dimopoulos et al, 2017; Palumbo et al., 2016; Lonial et al., 2016; Dimopoulos et al., 2016) Daratumumab is an immunoglobulin G1 kappa (IgG1k) human monoclonal antibody (mAb) that binds to a unique CD38 epitope on CD38-expressing cells with high affinity. It was developed by the immunization of human immunoglobulin transgenic mice with recombinant CD38 protein.(Sanchez et al., 2016) CD38 is a 46-kDa type II transmembrane glycoprotein that is highly expressed on MM cells.(McEllistrim et al., 2017) CD38 has various mechanisms including ectoenzymatic activity, receptor-mediated regulation of cell adhesion and signal transduction.(Malavasi et al., 2006) Preclinical studies have shown that daratumumab induces MM cell death through several mechanisms, including complement-dependent

cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and FcR mediated-crosslinking inducing apoptosis.(Sanchez et al., 2016) In a combined analysis of GEN501 and SIRIUS studies including 148 patients, the Overall Response Rate (ORR) was 31 %, and at a median follow-up of 14.8 months, the estimated Overall Survival (OS) was 19.9 months.(Usmani et al., 2015) These trials demonstrated that daratumumab is active as monotherapy in patients with heavily pre-treated and relapsed/refractory myeloma (RRMM) alongside maintaining its anti-myeloma activity in previously treatment refractory patients as evident by ORR 33 and 29.7 % in GEN501and SIRIUS, respectively.(Usmani et al., 2015) Preclinical studies have shown that Daratumumab in combination with other agents enhances the antimyeloma activity and now there are reported multiple phase II /III trials to study the same. These include data from the CASTOR and POLLUX trials of the combination of daratumumab and dexamethasone with bortezomib and lenalidomide, respectively, showing enhanced efficacy of these regimens in patients with early relapsed MM (2^{nd} or 3^{rd} line) and low minimal residual disease (MRD) states leading to the FDA approval of these regimens. Palumbo et al., 2016; Lonial et al., 2016; Dimopoulos et al., 2016)

Elotuzumab is a first-in-class humanized immunoglobulin G1 immunostimulatory monoclonal antibody targeted against signaling lymphocytic activation molecule F7 (SLAMF7, also called CS1 [cell-surface glycoprotein CD2 subset 1]), a glycoprotein expressed on myeloma and natural killer cells but not on normal tissues that enables selective killing of myeloma cells with minimal effects on healthy tissue.(His et al., 2008) The SLAM family is a subgroup of the immunoglobulin superfamily of receptors and consists of six members (SLAM, 2B4, Ly-9, NTB-A, CD94, and SLAMF7), all located on chromosome 1q23.(15) More than 95% of bone marrow myeloma cells express SLAMF7 in a manner that is independent of cytogenetic abnormalities.Hsi et al., 2008; Tai et al, 2008) Elotuzumab exerts a dual effect by directly activating natural killer cells and mediating antibody-dependent cell-mediated cytotoxicity through the CD16 pathway.(Collins et al., 2013) SLAMF7 mediates activating signals in natural killer cells by coupling with its adapter protein EAT-2. In myeloma cells, SLAMF7 signaling is compromised owing in part to the lack of EAT-2 expression; therefore, elotuzumab does not induce the proliferation of myeloma cells.(Guo et al., 2015; Perez-Quintero et al., 2014) In a single-group, phase 2 trial of elotuzumab in combination with lenalidomide and dexamethasone, this immunostimulatory activity translated into an improvement in progression-free survival in patients with relapsed or refractory multiple myeloma and followed by this randomized phase 3 trials were done leading to the FDA approval of Elotuzumab with lenalidomide and dexamethasone in patients with RRMM.(Dimopoulos et al., 2017)

1.13 Rationale of Elotuzumab after Daratumumab Treatment in MM

Daratumumab has emerged as a highly effective anti-MM agent as well as a partner to other already available anti-MM drugs including proteasome inhibitors and immunomodulatory drugs (IMiDs). This has lead to utilization of daratumumab earlier in the treatment paradigm of MM patients.(Dingli et al., 2017) On the other hand, there have been some questions regarding the optimal positioning of Elouzumab, which has a distinct mechanism of action than Daratumumab, and did not show any efficacy by itself. Furthermore, it was not

studied in patients who had been previously exposed significantly to IMiDs, which are used routinely early on in MM care and majority of patients that may become eligible for treatment with Elotuzumab may already have disease refractory to lenalidomide (full dose or maintenance dose). Thus, combining elotuzumab with another agent, pomalidomide in this case, and utilizing in patients who have had disease progression on daratumumab previously is a strategy that is warranted to understand how this FDA-approved agent will be optimally utilized as the therapeutic landscape of MM advances.

1.14 Trial Design

This will be a phase II, open label, prospective clinical trial in MM patients with disease previously treated utilizing any daratumumab-based regimen and disease progression noted while on the daratumumab-based regimen or within 60 days of discontinuation of daratumumab (daratumumab refractory). Such patients will be treated with a combination of elotuzumab, pomalidomide and dexamethasone, as previously presented.(San Miguel et al., 2016) The efficacy of elotuzumab in previously daratumumab-treated patients will help determine its appropriate role in treatment of patients with RRMM.

The dose schedule of Elotuzumab selected for the current trial is in accordance of several combination clinical trials that have been published with this agent since its FDA approval. Based on those trials, Elotuzumab is dosed weekly for the first 8 weeks and then is given as 20 mg/Kg dose every 4 weeks till disease progression or intolerable adverse events. (ref: Elo-pom-dex currently ongoing trial NCT#02654132)

2.0 Goals

2.1 Primary Goal

To determine the overall response rate (ORR) of utilizing elotuzumab, pomalidomide and dexamethasone in patients with disease refractory to daratumumab.

2.2 Secondary Goals

2.21 To determine percentage of patients achieving complete response (CR) with the elotuzumab combination.

2.22 To determine progression-free survival (PFS) for treatment with the elotuzumab combination.

2.23 To determine safety profile for treatment with the elotuzumab combination.

2.24 To determine the overall survival (OS) for patients receiving treatment with the elotuzumab combination.

3.0 Registration Patient Eligibility

3.1 Registration - Inclusion Criteria

3.11 Age ≥18 years

3.12 Diagnosis: Pathologically confirmed diagnosis of multiple myeloma and noted to have progressive disease (IMWG criteria as per Section 11.5)

3.13 At least one prior line of therapy.

3.14 Disease refractory to daratumumab as defined by disease progression while on or ≤ 60 days of completing treatment with a daratumumab-containing regimen as part of any prior line of therapy.

3.15 Measurable disease ≤ 14 days prior to registration (As per criteria in Section 11.1).

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

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

- Absolute neutrophil count (ANC) ≥1,000 cell/mm^3 without growth factor support
- Platelet ≥50,000 cells/mm^3 for patients who have bone marrow plasmacytosis <50% or ≥30,000 cells/mm^3 for patients who have bone marrow plasmacytosis of ≥50%
- Total bilirubin ≤1.5 x 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
- PT/INR/aPTT ≤1.5 x ULN OR if patient is receiving anticoagulant therapy and PT/INR or aPTT is within target range of therapy
- Calculated or measured creatinine clearance ≥30 ml/min (see Appendix II)

3.18 **Negative urine or serum pregnancy test done ≤14 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 Provide written informed consent.

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

3.19c Willing to follow the requirements of the {Revlimid®/Pomalyst®} REMS program.

3.2 Registration - Exclusion Criteria

3.21 Non-secretory MM or known AL amyloidosis

3.22 Clinically significant active infection requiring intravenous antibiotics (≤14 days prior to registration).

3.23 ≥Grade 3 neuropathy and/or POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

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

NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.25 Concurrent therapy considered investigational.
NOTE: Patients must not be planning to receive any radiation therapy (except localized radiation for palliative care that must be completed prior to starting Cycle 1, Day 1).

3.26 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women (lactating females are eligible provided that they agree not to breast feed while taking lenalidomide)
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.27 Other active malignancy ≤3 years prior to registration.
EXCEPTIONS:

- Adequately treated basal cell or squamous cell skin cancer
- Any in situ cancer
- Adequately treated Stage I or II cancer from which the patient is currently in complete remission, or

NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment for their cancer.

3.28 Major surgery ≤4 weeks prior to registration.

3.29a History of stroke/intracranial hemorrhage ≤6 months prior to registration.

3.29b Clinically significant cardiac illness including New York Heart Association (NYHA) Class III or Class IV heart failure (Appendix III), unstable angina pectoris, myocardial infarction within the past 6 months, or ≥Grade 3 cardiac arrhythmias noted ≤ 14 days prior to registration.

3.29c Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix VI).

3.29d Exhibiting clinical signs of meningeal involvement of multiple myeloma.

3.29e Known severe chronic obstructive pulmonary disease or asthma defined as forced expiratory volume (FEV1) in 1 second <60% of expected.

3.29f Prior exposure to elotuzumanb.

3.29g Prior history of disease refractory to pomalidomide.

3.29h 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.

3.29j 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.

4.0 Test Schedule

4.1 Test schedule for Multiple Myeloma

Tests and procedures		Active Monitoring Phase			
	≤ 14 days prior to registration	Cycle 1, Day 15	Prior to subsequent cycle/ treatment (≥ cycle 2) Day 1	During course of treatment (Day 15 of Cycle 2)	End of treatment (≤2 weeks after the final dose)
Window		±3 days	±3 days	±3 days	
Complete medical and disease history	X		X		X
Physical examination[1]	X		X		X
Performance status (ECOG scale)	X		X		X
Hematology group CBC w/diff	X	X	X	X	X
Chemistry group Sodium Chloride Potassium Magnesium Phosphate Uric acid BUN Glucose ALT/AST ALP Total protein Total bilirubin Direct bilirubin Albumin Serum creatinine Calcium LDH	X	X	X	X	X
PT/INR/aPTT	X				

Tests and procedures		Active Monitoring Phase			
	≤ 14 days prior to registration	Cycle 1, Day 15	Prior to subsequent cycle/ treatment (≥ cycle 2) Day 1	During course of treatment (Day 15 of Cycle 2)	End of treatment (≤2 weeks after the final dose)
Bone marrow aspirate/biopsy with standard testing (including but not limited to myeloma FISH and flow cytometry)[2]	X				X
Electrophoresis of serum and urine (SPEP/UPEP)	X		X[9]		X
Serum immunoglobulins[3]	X		X		X
Immunofixation serum and urine (IF)	X		X		X
Immunoglobulin free light chain (FLC)	X		X		X
Serum β2-microglobulin	X				X
PET/CT scan[4]	X				X
Adverse Event monitoring[5]	X	X	X	X	X
Pregnancy test[6]	X		X		
Registered in the POMALYST REMS™ program[7]	X				
Pill Diary[8]			X		X

Cycle = 28 days

1. To include blood pressure, pulse rate, temperature, weight. Height to be documented ≤14 days prior to registration
2. Standard of care procedure: ≤28 days prior to registration, at the time of disease progression, and if considered clinically indicated at any other time during the study. **NOTE: Repeat biopsy at Cycle 1, Day 1 if biopsy was not completed ≤ 28 prior to registration.**
3. Serum immunoglobulins to include IgG, IgA and IgM for all patients and IgD or IgE where clinically indicated.
4. A PET scan should be done≤ 28 days prior to registration, at the time of disease progression, and if considered clinically necessary. **NOTE: Repeat PET/CT at Cycle 1, Day 1 if PET/CT was not completed ≤ 28 prior to registration prior to registration.**
5. During the course of treatment and at end of treatment visit. The patient should be contacted by a nurse 30 days after the last dose of study treatment (or at the time of initiation of subsequent treatment if started before 30 days) to check if the patient has experienced any late adverse events. Grade 3 or higher adverse events at least possibly related to study treatment and deaths due to any cause should be

reported as a late adverse event on the survival follow-up form if they were not already reported on the Adverse Event form for the last cycle and they occurred prior to any subsequent treatment and 30 days post-end of treatment

6. For females of childbearing potential, a negative pregnancy test (urine or serum) must be documented ≤ 14prior to registration on the study and thereafter in accordance with the POMALYST REMS™ program. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
7. ≤ 14 days prior to registration.
8. To be collected at the end of every cycle of therapy while the patient is receiving pomalidomide or oral dexamethasone.
9. UPEP testing required at baseline only. Subsequent testing will be as needed per physician discretion.

4.2 Survival Follow-up

	Survival Follow-up				
	q. 3 months until PD or subsequent treatment	At PD or subsequent therapy	After PD or subsequent therapy q. 6 months	Death	New Primary
Survival Follow-up	X	X	X	X	At each occurrence

1. If a patient is still alive 3 years after registration, no further follow-up is required.

5.0 Stratification Factors OR Grouping Factor:

None.

6.0 Registration

6.1 Registration (Step 1):

6.11 Registering a patient

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. 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 the MCCC Registration Office 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 MCCC web page (http://ccswww/training/index.html) 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 the MCCC Registration Office (507) 284-2753. If the patient was fully registered, the MCCC Registration Office 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) at the Registration Office (fax: 507-284-0885). 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 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic Florida under the supervision of a medical oncologist/hematologist.

6.5 Treatment start

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

6.6 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.7 Baseline symptoms

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

6.8a Study drug

Study drug is available on site.

6.8b 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

7.11 Treatment medication table (Cycles 1-2)

Agent	Dose Level	Route	Day
Elotuzumab	10 mg/Kg*	IV	1, 8, 15, 22
Pomalidomide	4 mg	PO	1-21
Dexamethasone	40 mg**	IV	1, 8, 15, 22

Cycle length = 28 days, Treatment Window (+/- 3 days)
Dexamethasone to be administered IV 45-90 mins prior to elotuzumab infusions on the days both are being administered to patients
*Any dose-adjustments will be made as per the prescriber information. Elotuzumab administration as per prescriber information and institutional guidelines.
**If patient age ≥ 75, dexamethasone dose will be 20 mg.

7.12 Treatment medication table (Cycles 3 and onward)

Agent	Dose Level	Route	Day
Elotuzumab	20 mg/Kg*	IV	1
Pomalidomide	4 mg	PO	1-21
Dexamethasone	40 mg**	IV	1
Dexamethasone	40 mg**	PO	8, 15, 22

Cycle length = 28 days, Treatment Window (+/- 3 days)
Dexamethasone to be administered IV 45-90 mins prior to elotuzumab infusions on the days both are being administered to patients
*Any dose-adjustments will be made as per the prescriber information. Elotuzumab administration as per prescriber information and institutional guidelines.
**If patient age ≥ 75, dexamethasone dose will be 20 mg.

7.13 Infusion rate for elotuzumab

Cycle 1, Dose 1		Cycle 1, Dose 2		Cycle 1, Dose 3, 4 and all Subsequent Cycles
Time Interval	Rate	Time Interval	Rate	Rate
0-30 min	0.5 ml/min	0-30 min	3 ml/min	5 ml/min
30-60 min	1 ml/min	30 min or more	4 ml/min	
60 min or more	2 ml/min			

7.2 Treatment by local medical doctor (LMD)

Treatment by a local medical doctor (LMD) is not allowed.

7.3 Overdose

Any dose of study drug in excess of the amount provided in the protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event

criterion must be reported as a Serious Adverse Event in the appropriate timeframe and documented as clinical sequelae to an overdose.

There has been no experience of overdosage with elotuzumab in clinical studies. There is no known specific antidote for elotuzumab overdose. In the event of an overdose, the subject should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

Refer to section 10 for further information regarding AE reporting.

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 elotuzuumab and/or pomalidomide and/or dexamethasone as per which of these drugs the adverse event is attributable to.

→ ***ALERT:*** ***ADR reporting may be required for some adverse events (See Section 10.0)*** ←

8.1 Recommended Dose Modifications (Based on Adverse Events in Tables 8.*2* and 8.3 and treating physician assessment)

8.11 Dose Modifications (Cycle 1 and 2)

Dose Level	Elotuzumab (Cycle 1 and 2)	Pomalidomide	Dexamethasone
1*	10 mg/kg	4 mg	40 mg**
-1	Discontinue	3 mg	20 mg
-2		2 mg	12 mg
-3		Discontinue	8 mg
-4			Discontinue

*Dose level 1 refers to the starting dose.

** If patient age ≥ 75, dexamethasone dose will be 20 mg.

8.12 Dose Modifications (Cycle 3 and beyond)

Dose Level	Elotuzumab (Cycle 3 and beyond)	Pomalidomide	Dexamethasone
1*	20 mg/kg	4 mg	40 mg**
-1	10 mg/kg	3 mg	20 mg
-2	Discontinue	2 mg	12 mg
-3		Discontinue	8 mg
-4			Discontinue

*Dose level 1 refers to the starting dose.
** If patient age ≥ 75, dexamethasone dose will be 20 mg.

NOTES:

- Missed doses for pomalidomide are to be omitted rather than made up, unless the dose was forgotten and remembered on the same day, in which case the dose can be taken that day. Any doses missed on a particular day are not to be made up the next day. Doses that are considered to be vomited are not to be made up and a mention about the time of dose and time of vomiting episode should be made in the pill diary.
- Elotuzumab may be administered within ±1 day of the scheduled dose if there are any logistical challenges (holiday, patient transport or other logistics, scheduling availability, etc.)
- If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

- Reductions are based on the dose given in the preceding cycle and are based on toxicities with an attribution of possible, probable, or definite that were observed since the prior toxicity evaluation.
- Patients may continue on treatment with any two of the study drugs (elotuzumab or pomalidomide or dexamethasone) in case one of the agents has to be permanently discontinued. If a patient on treatment must discontinue two or all three drugs in the combination permanently, they should be removed from the protocol therapy and proceed to survival follow-up.
- A dose omit/delay of ≤28 days for any of the drugs is allowed. If a patient cannot be administered a dose of two or all three drugs in the study treatment for >28 days due to adverse events or any other reason, the patient should be removed from the study treatment and go to survival follow-up.

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

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

8.2 Dose Modifications for pomalidomide based on adverse events

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Blood and lymphatic system disorders	Anemia	pomalidomide	Omit dose if Grade 4 and follow CBC weekly until ≤Grade 2. •If anemia resolves to ≤Grade 2, resume dose at one level lower •If the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on elotuzumab and dexamathesone. Discontinue pomalidomide.
	Febrile Neutropenia	pomalidomide	Omit dose if ≥ Grade 3 and follow CBC weekly. • If neutropenia has resolved to ≤Grade 2, resume dose at same level with GCSF support (See Section 9.2)
Cardiac disorders	Sinus Bradycardia/ other cardiac arrhythmia	pomalidomide	Omit dose if Grade 2 and follow weekly until resolution. • If AE resolves to ≤Grade 1, reduce dose by one dose level and continue therapy. If AE is ≥ Grade 3, discontinue pomalidomide and continue elotuzumab and dexamethasone.
Immune System Disorders	Allergic Reaction	pomalidomide	Omit dose if Grade 2-4 and follow weekly until resolution. • If AE resolves to ≤Grade 1, reduce dose by 1 level and continue therapy.
	Anaphylaxis	pomalidomide	Discontinue study treatment if Grade 3-4 and go to survival follow-up.
Investigations	Neutrophil count decreased	pomalidomide	Omit dose if Grade 4 and follow CBC weekly until ≤ Grade 1. •If neutropenia has resolved to ≤Grade 2, resume dose at one level lower *If, after pomalidomide has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on elotuzumab and dexamathesone. Discontinue pomalidomide.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
	Platelet count decreased	pomalidomide	Omit dose if Grade 4 and follow CBC weekly until ≤ Grade 1. • If thrombocytopenia ≤30,000/mm3 occurs, reduce dose by one dose level and continue therapy when platelet count is ≥30,000/mm3. •If after pomalidomide has been omitted, and the AE does not return to ≤Grade 1 within 4 weeks, then the patient may continue on elotuzumab and dexamathesone. Discontinue pomalidomide.
Skin and subcutaneous tissue disorders	Erythema multiforme	pomalidomide	Discontinue study treatment if ≥Grade 3 and continue to survival follow-up.
	Skin ulceration	pomalidomide	Discontinue study treatment if ≥Grade 2 and continue to survival follow-up.
	Other:Non-blistering rash	pomalidomide	Omit dose if Grade 3 and follow weekly until resolution. • If AE resolves to ≤Grade 2 continue therapy •Discontinue study treatment if Grade 4 and continue to survival follow-up.
Vascular Disorders	Thromboembolic event		Omit dose if ≥ Grade 3 and start anticoagulation; restart at investigator's discretion (maintain dose level)
Other AEs	Non-hematologic AE assessed as related to lenalidomide	pomalidomide	Omit dose if ≥Grade 3 and follow weekly until resolution • If the AE resolves to ≤Grade 2, implement one dose reduction step and continue therapy (per Table 8.1)

** 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.

If pomalidomide has been omitted and the toxicity does not return to ≤Grade 2 within 28 days, the patient may discontinue any further treatment with pomalidomide and proceed with the other agents on the protocol.

8.21 Pomalidomide dose adjustment for renal function

Pomalidomide dose will be adjusted as per standard of care guidelines in the prescribing information of pomalidomide for multiple myeloma patients. Patients with creatinine clearance (CrCl) <30 ml/min noted while on treatment and not considered secondary to

disease progression will have dose modifications as per the clinical judgement. Patients with baseline CrCl <30 ml/minute are not eligible for this study (Appendix II).

8.3 Elotuzumab Dose Modifications (**NOTE:** Only if any of the following criteria are met and the event cannot be ascribed to pomalidomide or to any other concurrent medication that the patient may be on, the elotuzumab infusion must be held/omitted to allow for recovery from toxicity).

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION*
Blood and lymphatic system disorders	Febrile Neutropenia	elotuzumab	If AE is ≥ Grade 3, hold if Day 1. Omit if days 8, 15, or 22 during Cycles 1 & 2. • Hold/omit elotuzumab ** until recovery • May restart at same dose at the next planned dosing date.
Investigations	Neutrophil count decreased	elotuzumab	If AE is Grade 4 and lasting >7 days, hold if Day 1. Omit if days 8, 15, or 22 during Cycles 1 & 2. • Hold/omit elotuzumab ** until recovery to Grade ≤1 or baseline • May restart at same dose at the next planned dosing date.
Investigations	Platelet count decreased	elotuzumab	If AE is Grade 4 and lasting >7 days, hold if Day 1. Omit if days 8, 15, or 22 during Cycles 1 & 2. • Hold/omit elotuzumab ** until recovery to Grade ≤1 or baseline • May restart at same dose at the next planned dosing date.
Gastrointestinal disorders	Nausea	elotuzumab	If AE is ≥ Grade 3and persistent for >7 days despite optimal antiemetic therapy, hold if Day 1. Omit if days 8, 15, or 22 during Cycles 1 & 2. • Hold/omit elotuzumab ** until recovery to Grade ≤1 or baseline • May restart at same dose at the next planned dosing date.
	Vomiting	elotuzumab	If AE is ≥ Grade 3and persistent >7 days despite optimal antiemetic therapy, hold if Day 1. Omit if days 8, 15, or 22 during Cycles 1 & 2. • Hold/omit elotuzumab ** until recovery to Grade ≤1 or baseline • May restart at same dose at the next planned dosing date.
	Diarrhea	elotuzumab	If AE is ≥ Grade 3and persistent for >7 days despite antidiarrheal therapy, hold if Day 1. Omit if days 8, 15, or 22 during Cycles 1 & 2. • Hold/omit elotuzumab ** until recovery to Grade ≤1 or baseline • May restart at same dose at the next planned dosing date.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION*
Other (Non-hematologic)****	Any other Grade 4 AE or any recurrent Grade 3 AE that was present at baseline or lasts for >7 days after the last administration of elotuzumab	elotuzumab	Hold if Day 1. Omit if days 8, 15, or 22 during Cycles 1 & 2. • Hold/omit elotuzumab ** until recovery to Grade ≤1 or baseline • May restart at same dose at the next planned dosing date.

* 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.
  Additional Adverse Events:

  ** If elotuzumab is omitted in the middle of the cycle and the toxicity resolves, patient can re-start the drug but the days of drug treatment missed do not need to be caught-up and can be omitted in order to maintain the cycle schedule.
  - Dose omission: elotuzumab may be omitted for adverse event considerations for a maximum of 28 consecutive days. Study medication should be discontinued permanently in the event of AE lasting more than 28 days.
  - If multiple adverse events are seen, administer dose based on the greatest reduction required by any single adverse event observed.
  - Dose modifications are for adverse events attributed to study treatment only. Dose modifications are not required for adverse events if they are deemed unrelated and/or unlikely related to study treatment.
  - Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
  - Patients can continue pomalidomide and dexamethasone if elotuzumab is held/omitted for AEs on Day 1 or during the cycle.

  **** If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO) should be considered. Consider Pneumocystis pneumonia or viral pneumonitis. Patients who experience a deep vein thrombosis (DVT), pulmonary embolus (PE), or other clotting event should have all study drugs temporarily omitted while full-dose anticoagulation is initiated (other than warfarin or other Vitamin K antagonist). There should not be a delay of more than 28 days in reinitiating the study treatment.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire remaining length of the study treatment.

8.4 Dexamethasone Dose Modifications

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION
Cardiac Disorders	Sinus bradycardia Grade 3 or 4	dexamethasone	Omit dose and follow at least weekly If the AE resolve to ≤2, implement one dose reduction step and continue therapy
General disorders and administration site conditions	Edema ≥Grade 3 (limiting function and unresponsive to therapy or anasarca)	dexamethasone	Diuretics as needed, and decrease dexamethasone dose by 1 dose level If edema persists despite above measures, decrease dose another dose level Discontinue dexamethasone and do not resume if symptoms persist despite second reduction. Can continue elotuzumab and pomalidomide.
Gastrointestinal disorders	Lower gastrointestinal hemorrhage OR Upper gastrointestinal hemorrhage	dexamethasone	Discontinue dexamethasone Can continue elotuzumab and pomalidomide.
	Pancreatitis ≥Grade 3	dexamethasone	Discontinue dexamethasone
	Dypepsia, Gastric ulcer, duodenal ulcer, OR Gastritis ≥Grade 3	dexamethasone	Omit dexamethasone until symptoms adequately controlled Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, discontinue dexamethasone Can continue elotuzumab and pomalidomide.
Other	Non-hematologic AE assessed ≥Grade 3	dexamethasone	Omit dose and follow at least weekly If the AE resolves to ≤Grade 2, implement one dose reduction step and continue therapy
Psychiatric disorders	Confusion≥Grade 3	dexamethasone	Omit dexamethasone until symptoms resolve Restart with one dose level reduction If symptoms persist despite above measures, discontinue dexamethasone Can continue elotuzumab and pomalidomide.

* 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.

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.

9.5 Biosphosphonates

Patients may receive concurrent treatment with a bisphosphonate.

9.6 Thrombophylaxis

Due to the increased risk of deep vein thrombosis (DVT) for multiple myeloma patients, thromboprophylaxis is to be used as standard of care on this regimen according to the International Myeloma Working Group guidelines (http://jco.ascopubs.org/content/32/6/587.full).(21)

9.7 Herpes Zoster Prophylaxis

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis with acyclovir 400 mg PO BID should be used while on study therapy and for 3 months beyond the end of therapy.

9.8 Prohibited Medications

The following medications are not permitted during the trial:

- Any other investigational treatment
- Any cytotoxic chemotherapy

- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- Any external beam radiotherapy. **NOTE:** Radiation therapy administered with palliative intent to control localized symptoms from MM is permitted provided the symptoms are not considered due to disease progression.

9.9 Concomitant medications

Any systemic anti-myeloma therapy or steroids other than those prescribed by the protocol are prohibited while on protocol therapy. Guidelines for selection and use of other concomitant medications should be derived from the dexamethasone, elotuzumab, and pomalidomide prescribing information. Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study.

9.10 Guidelines for prevention of infusion reactions

Pre-infusion Medications: On elotuzumab infusion days, subjects will receive the following medications 45 to 90 minutes prior to infusion in addition to dexamethasone outlined in section 7.0:

- Acetaminophen 650-1000 mg orally
- Diphenhydramine (or comparable H1 blocker) 25 to 50 mg orally or intravenously
- Famotidine (or comparable H2 blocker) 20 mg orally or intravenously

9.11 Guidelines for management of infusion reactions

Subjects should be carefully observed during elotuzumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions occurring and resources necessary for resuscitation must be available at the bedside.

If a Grade 2 or higher infusion reaction occurs during elotuzumab administration, interrupt the infusion and institute appropriate medical and supportive measures (antiemetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen, epinephrine, bronchodilators, or other supportive measures as indicated). Upon resolution to Grade 1 or lower, restart at 0.5 mL per minute and gradually increase at a rate of 0.5 mL per minute every 30 minutes as tolerated to the rate at which the infusion reaction occurred. Resume the escalation regimen if there is no recurrence of the infusion reaction (see Table 7.13).

In patients who experience an infusion reaction, monitor vital signs every 30 minutes for 2 hours after the end of the elotuzumab infusion. If the infusion reaction recurs, stop the elotuzumab infusion and do not restart on that day.

Infusion reactions after the completion of elotuzumab infusion: Should a Grade ≥ 2 infusion reaction occur following completion of an elotuzumab infusion, the subject should be treated as clinically indicated with 1 or more of the following medications or interventions: diphenhydramine, acetaminophen, hydrocortisone, H2 inhibitor, leukotriene inhibitor, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

Elotuzumab infusions on subsequent weeks after a prior Grade ≥ 2 infusion reaction: Subjects with prior Grade 2 or higher infusion reactions should have future infusions started at 0.5 mL/min and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes, See section 7.13).

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:
All 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 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 in an expedited manner[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
Gastrointestinal Disorders	Diarrhea	≤Grade 3
	Nausea	≤Grade 3
	Vomiting	≤Grade 3
General disorders and administration site conditions	Fatigue	≤Grade 3
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.

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 should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. 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
Blood and lymphatic system disorders	Anemia		X
General disorders and administration site conditions	Maculopapular Rash	X	X
	Infusion related reaction		X
	Fatigue	X	X
Investigations	Neutrophil count decreased		X
	Platelet count decreased		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.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities.

10.81 Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*. Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v5.0.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to section 10.8 above.

11.0 Treatment Evaluation

The International Myeloma Working Group (IMWG) uniform response criteria (Kumar et al, 2016) 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 be 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 ≥1 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

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 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

Table 11.2

Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])

On Study Baseline Value	SPEP[4]	24 hr UPEP[2]	Ig FLC	BM Bx
Serum M-protein ≥1 g/dl, and urine M-protein≥ 200 mg/24 hrs	X	X		
Serum M-protein ≥ 1 g/dl, but urine M-protein < 200 mg/24 hrs	X			
Serum M-protein <1 g/dl, and urine M-protein≥ 200 mg/24 hrs		X		
Serum M-protein < 1 g/dl, urine M-protein < 200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X	
Serum M-protein < 1 g/dl, urine M-protein< 200				X[3]

mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow ≥30% plasma cells				

[1] ***SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy*** *are required to document CR regardless of registration values, and in addition* ***FLC*** *measurement and* ***bone marrow immunophenotyping*** *is required to document sCR.*

[2] *For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category*

[3] *At a minimum, a bone marrow biopsy should be repeated every 3 months until documented response. Bone marrow biopsy results do not need to be repeated after documented response.*

[4] *If serum M-protein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.*

11.3 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.

Appropriate tests required to document and confirm response are listed in Table 11.2

11.4 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.

11.5 Response and progression

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]
Very Good Partial	• Serum and urine M-protein detectable by immunofixation but not

Response (VGPR)	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
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]
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, ≥50% 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] 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

[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 MM risk categories (As per Appendix IV): High vs. standard/intermediate.

12.2 Immediately prior treatment was daratumumab-based: yes vs. no

12.3 Parameters followed for hematologic response: serum monoclonal protein ≥1 g/dL and urine monoclonal protein ≥200 mg/24 hours vs. serum monoclonal protein ≥1g/dL only vs. urine monoclonal protein ≥200 mg/24 hours only vs. serum immunoglobulin free light chain ≥10 mg/dL. Distinguish between SPEP measurements versus quantitative IgA measurements versus quantitative IgD measurements for serum monoclonal protein.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

Reason Off Treatment (from the Off Treatment Form)	*Go to CFU, SFU, or end folder rollout*
1 = Treatment (Intervention) Completed Per Protocol Criteria	N/A
2 = Patient Withdrawal/Refusal After Beginning Protocol Therapy (Intervention)	SFU
3 = Adverse Events/Side Effects/Complications	SFU
4 = Disease Progression, Relapse During Active Treatment (Intervention)	SFU
5 = Alternative Therapy	SFU
6 = Patient Off-Treatment (Intervention) For Other Complicating Disease	SFU
7 = Death On Study	No follow-up
8 = Other	SFU
10 = Disease Progression Before Active Treatment (Intervention)	No follow-up
24 = Patient Withdrawal/Refusal Prior To Beginning Protocol Therapy (Intervention)	No follow-up

13.1 Continuation of treatment

Patients who are sCR, CR, VGPR, PR, MR, or SD (or usCR, uCR, uVGPR, uPR, uMR will continue treatment per protocol.

13.2 Progressive disease (PD)

Patients who develop PD while receiving therapy will go to the survival follow-up phase.

13.3 Off protocol treatment

Patients who go off protocol treatment for reasons other than PD will go to the survival follow-up phase per Section 4.0.

13.9b 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 and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.9c 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.

13.9d 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 Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

None.

15.0 Drug Information

15.1 Dexamethasone commercial supply (Decadron, Hexadrol, and various)

15.11 **Formulation and storage (injection)**: Dexamethasone sodium phosphate is supplied as 4mg/ml IV solution in 5ml vials. Store intact vials at controlled room temperature, do not refrigerate. Protect from heat and light.

Formulation and storage (tablets): Dexamethasone tablets should be stored at room temperature and are stable for at least 2 years. Dexamethasone should be given as a single daily dose in the a.m. after breakfast.

15.12 **Preparation**: The sterile solution from the vial may be further diluted in D5W or NS (refer to the treatment section of the protocol).

15.13 **Stability**: Refer to expiration date on the vial.

15.14 **Administration**: IV push or infusion (see treatment section of the protocol).

15.15 **Known potential toxicities**: 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.

15.16 **Drug procurement**: Drug will be procured from the commercial supply of Dexamethasone.

15.17 **Nursing guidelines:**

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

15.172 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.

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

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

15.175 Monitor blood glucose frequently.

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

15.177 Advise patient that easy bruising is a side effect.

15.2 Elotuzumab (Empliciti™)

15.21 **Background**: Elotuzumab is an antineoplastic agent that is an antibody against the SLAMF7 antigen expression on cells including multiple myeloma.

15.22 **Formulation**: Elotuzumab drug product is a 300 mg or 400 mg lyophilized powder in a single-dose vial for reconstitution.

15.23 **Preparation and storage**: Once the dose is calculated (mg), determine the number of vials needed for the 10 mg/kg dosage based on patient weight. The volume of sterile water for injection (SWFI) needed for reconstitution should be calculated as follows:

Reconstitution Instructions for EMPLICITI			
Strength	Amount of Sterile Water for Injection, USP Required for Reconstitution	Deliverable Volume of Reconstituted EMPLICITI in the Vial	Postreconstitution Concentration
300 mg vial	13 ml	12 ml*	25 mg/ml
400 mg vial	17 ml	16 ml*	25 mg/ml
*After reconstitution, each vial contains overfill to allow for withdrawal of 12 mL (300 mg) and 16 mL (400 mg), respectively.			

Reconstitution: Aseptically reconstitute each EMPLICITI vial with a syringe of adequate size and a less than or equal to 18-gauge needle (e.g., 17-gauge). A slight back pressure may be experienced during administration of the Sterile Water for Injection, USP, which is considered normal. Hold the vial upright and swirl the solution by rotating the vial to dissolve the lyophilized cake. Invert the vial a few times in order to dissolve any powder that may be present on top of the vial or the stopper. Avoid vigorous agitation. DO NOT SHAKE. The lyophilized powder should dissolve in less than 10 minutes. After the remaining solids are completely dissolved, allow the reconstituted solution to stand for 5 to 10 minutes. The reconstituted preparation results in a colorless to slightly yellow, clear to slightly opalescent solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the solution if any particulate matter or discoloration is observed.

Dilution: Once the reconstitution is completed, withdraw the necessary volume for the calculated dose from each vial, up to a maximum of 16 mL from 400 mg vial and 12 mL from 300 mg vial. Further dilute with 230 mL of either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, into an infusion bag made of polyvinyl chloride or polyolefin. The volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP can be adjusted so as not to exceed 5 mL/kg of patient weight at any given dose of EMPLICITI. Complete the EMPLICITI infusion within 24 hours of reconstitution of the EMPLICITI lyophilized powder. If not used immediately, the infusion solution may be stored under refrigeration conditions: 2°C to 8°C (36°F-46°F) and protected from light.

15.24 **Administration**: Intravenous (IV) infusion

Administer the entire EMPLICITI infusion with an infusion set and a sterile, nonpyrogenic, low-protein-binding filter (with a pore size of 0.2 to 1.2 micrometer) using an automated infusion pump. Initiate EMPLICITI infusion at a rate of 0.5 mL per minute. The infusion rate may be increased in a stepwise fashion as described in Table below if no infusion reactions develop. The maximum infusion rate should not exceed 5 mL per minute.

<table>
<tr><td colspan="5">Infusion Rate for EMPLICITI</td></tr>
<tr><td colspan="2">Cycle 1, Dose 1</td><td colspan="2">Cycle 1, Dose 2</td><td>Cycle 1, Dose 3, 4 and all Subsequent Cycles</td></tr>
<tr><td>Time Interval</td><td>Rate</td><td>Time Interval</td><td>Rate</td><td>Rate</td></tr>
<tr><td>0-30 min</td><td>0.5 ml/min</td><td>0-30 min</td><td>3 ml/min</td><td rowspan="3">5 ml/min</td></tr>
<tr><td>30-60 min</td><td>1 ml/min</td><td rowspan="2">30 min or more</td><td rowspan="2">4 ml/min</td></tr>
<tr><td>60 min or more</td><td>2 ml/min</td></tr>
</table>

Adjust the infusion rate following a Grade 2 or higher infusion reaction (as per the package insert). Do not mix EMPLICITI with, or administer as an infusion with, other medicinal products. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of EMPLICITI with other agents.

15.25 **Pharmacokinetic Information**:

Elotuzumab exhibits nonlinear pharmacokinetics (PK), indicative of target mediated clearance. The administration of the recommended 10 mg/kg of Elotuzumab regimen with Lenalidomide and Dexamethasone is predicted to result in geometric mean (CV%) steady-state trough concentrations of 194 µg/mL (52%).

The clearance of Elotuzumab decreased from a geometric mean (CV%) of 17.5 (21.2%) to 5.8 (31%) mL/day/kg with an increase in dose from 0.5 (i.e., 0.05 times the recommended dosage) to 20 mg/kg (i.e., 2 times the recommended dosage). When Elotuzumab is administered with lenalidomide and dexamethasone, approximately 97% of the maximum steady-state concentration is predicted to be eliminated with a geometric mean (CV%) of 82.4 (48%) days.

Clinically significant differences were not observed in the PK of Elotuzumab based on age (37 to 88 years) sex, race, baseline lactate dehydrogenase, albumin, renal imapairment(creatinine clearance (CLcr) 15 to 89 mL/min), end-stage renal disease (CLcr <15mL/min) with or without hemodialysis, and mild heptic impairment(total bilirubin ≤ upper limit of normal (ULN) and aspartate transaminase (AST)>ULN OR total bilirubin 1 to 1.5 times the ULN and AST any value) to severe (total bilirubin > 3 times the ULN and AST any value) hepatic impairment is unknown.

The clearance of Elotuzumab increased with increasing body weight supporting a weight based dose.

Half-life elimination ~97% of the maximum steady-state concentration is expected to be eliminated with a geometric mean (CV%) of 82.4 days.

15.26 Known Potential Toxicities:

- **Very Common (≥10%)**
  Cardiovascular: Decreased heart rate, increased heart rate, altered blood pressure
  Central nervous system: Fatigue, peripheral neuropathy, headache
  Endocrine & metabolic: Hyperglycemia, hypocalcemia, hypoalbuminemia, decreased serum bicarbonate, hyperkalemia, weight loss
  Gastrointestinal: Diarrhea, constipation, decreased appetite, vomiting
  Hematologic & oncologic: Lymphocytopenia, leukopenia, thrombocytopenia
  Hepatic: Increased serum alkaline phosphatase
  Immunologic: Immunogenicity
  Infection- Infection, opportunistic infection, herpes zoster, fungal infection
  Neuromuscular & skeletal: Limb pain
  Ophthalmic: Cataract
  Respiratory: Cough, nasopharyngitis, upper respiratory tract infection, pneumonia, oropharyngeal pain
  Miscellaneous: Fever, infusion related reaction
- **Common (1 to <10%)**
  Cardiovascular: Chest pain, pulmonary embolism
  Central nervous system: Hypoesthesia, mood changes
  Dermatologic: Night sweats
  Hematologic & oncologic: Second primary malignant neoplasm, malignant neoplasm of skin, solid tumor, anemia, malignant neoplasm
  Hepatic: Hepatotoxicity
  Hypersensitivity: Hypersensitivity
  Renal: Acute renal failure
  Respiratory: Respiratory tract infection
- **Infusion-related reactions (IRR):** IRRS were reported in approximately 10% of patients treated with Elotuzumab with Lenalidomide and Dexamethasone. All reports of infusion rection were Grade 3 or lower. Grade 3 infusion reactions occurred in 1 % of patients. The most common symptoms of IRRs included fever, chills and hypertension. Bradycardia and hypotension also developed during infusions.
  In the trial, 5% of patients required interruption of the administration of Elotuzumab for a median of 25 minutes due to infusion reactions, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had them during the first dose.
  Administer premedication consisting of dexamethasone, antihistamines (H1 and H2 blockers) and acetaminophen prior to Elotuzumab infusion. Interrupt Elotuzumab for Grade 2 or higher infusion reactions and institute appropriate medical management

15.27 **Drug Procurement**: Drug will be procured from the commercial supply of elotuzumab.

15.28 **Special Populations**:

- **Geriatric use:** Of the 646 patients across treatment groups in the randomized trial in multiple mmyeloma, 57% were 65 years of age or

older. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age)

- **Renal impairment:** CrCl ≤89 mL/minute. There are no dosage adjuments provided in the manufacturer's labelling; however, based on pharmacokinetics, dosage adjustment is not likely necessary.
- **Hepatic Impairment:**
  Mild (total bilirubin ≤ULN and AST >ULN **or** total bilirubin 1 to 1.5 times ULN and any AST) impairment: There are no dosage adjustments provided in the manufacturer's labeling; however, based on pharmacokinetics, dosage adjustment is not likely necessary.

  Moderate (total bilirubin >1.5 to 3 times ULN and any AST) to severe (total bilirubin >3 times ULN and any AST) impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

  Hepatotoxicity during treatment: Grade 3 or higher transaminase elevations: Withhold treatment; may consider continuing treatment after liver enzymes return to baseline

15.29 **Nursing Guidelines**

15.291 See section 15.24 for specific administration times and rates based on cycle/dose#.

15.292 While no formal drug to drug interactions have been done, in theory elotuzumab may enhance the effects of other immunosuppressants agents and decreased the effectiveness of immune stimulant (see section 15.26 for more detail)

15.293 Agent may cause changes in heartrate, including bradycardia or tachycardia. Instruct patient to report any palpitations/fast heartrate or symptoms of bradycardia (fatigue/syncope) to the study team immediately.

15.294 Gastrointestinal side effects can be seen, including diarrhea, constipation and vomiting. Treat symptomatically and monitor for effectiveness.

15.295 Monitor CBC w/diff as cytopenias can be seen. Instruct patient to reports any signs or symptoms of infection and/or bleeding to the study team.

15.296 Monitor LFT's.

15.297 Monitor for infusion related reactions and have emergency equipment available. Administer emegerency medications as ordered and monitor for their effectiveness.

15.298 Monitor creatinine, as rarely renal failure can happen.

15.3 Pomalidomide (Pomalyst®)

15.31 **Background**: Pomalidomide 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.

15.32 **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.

15.33 Placebo capsules for pomalidomide are available to use in blinded studies. The placebo capsules contain microcrystalline cellulose.

Pomalidomide capsules and pomalidomide placebo 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.

15.33 **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 drug for one month of therapy may be dispensed.

15.34 **Administration:** Pomalidomide is administered by mouth at approximately the same time each day. Pomalidomide should be taken without food (at least 2 hours before or 2 hours after a meal). 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.

15.35 **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.

Pomalidomide is metabolized primarily by the liver. Following single dose administration, the AUC of pomalidomide increased 51%, 58%, and 72% in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. Dose adjustment is recommended in patients with hepatic impairment.

For patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose is 3 mg daily (25% dose reduction). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose is 2 mg (50% dose reduction)

15.36 **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.

15.37 **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.

15.38 **Drug procurement:**

Drug will be procured from the commercial supply of pomalidomide.

15.39 **Nursing Guidelines**

15.191 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.

15.192 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).

15.193 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.

15.194 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.

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

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

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

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

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

15.199b 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.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a phase II study of elotuzumab, pomalidomide and dexamethasone in patients with multiple myeloma refractory to daratumumab. This study is designed to assess the overall response rate using a one stage phase II study design with an interim analysis.

16.11 Primary Endpoint: The primary endpoint of this study is the overall response rate. A response is defined as a PR,VGPR, CR, or sCR noted as the objective status on two consecutive evaluations. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.12 Sample Size: The one stage study design with an interim analysis to be used is fully described below. A minimum of 17 and a maximum of 37 evaluable patients will be accrued total onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons for a total of 41 patients overall.

16.13 Accrual Rate and Study Duration: The anticipated accrual rate is 2 evaluable multiple myeloma patients per month. Therefore, the accrual period for this phase II study is expected to be about 2 years. The maximum total study duration is expected to be approximately 5 years, or until the last patient accrued has been observed for at least 3 years after registration.

16.2 Statistical Design:

16.21 Decision Rule:
The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 20% (based on data from quad- and penta-refractory disease data in recent clinical trials), and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 40%. The following one–stage design with an interim analysis is based on a two-stage Simon optimum design(23) and requires 37 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 20%.

16.211 Interim Analysis: Enter 17 evaluable patients into the study. If 3 or fewer successes are observed in the first 17 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if the number of successes is at least 4, we will continue accrual.

16.212 Final Decision Rule: Enter an additional 20 evaluable patients into the study. If 10 or fewer successes are observed in the first 37 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 11, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies in this population.

16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

16.214 NOTE: We will not suspend accrual at the interim analysis to allow the first 17 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.22 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .09, i.e. there is a 9% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping at the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.20	0.25	0.30	0.35	0.40
Then the probability of declaring that the regimen warrants further study is…	0.09	0.28	0.54	0.76	0.90
And the probability of stopping at the interim analysis is…	0.55	0.35	0.20	0.10	0.05

16.23 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 trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when all patients have been followed for at least 6 cycles or have discontinued study treatment prior to completing 6 cycles.

16.31 Primary Outcome Analysis:

16.311 Definition: The primary endpoint of this trial is the overall response rate. A response is defined as a PR,VGPR, CR, or sCR noted as the objective status on two consecutive evaluations. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-

five percent confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.(24)

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.32 Secondary Outcome Analyses

16.321 The complete response rate will be estimated by the number of patients who achieve a sCR or CR divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true complete response rate will be calculated.

16.322 Progression-free survival time is defined as the time from registration to the time of progression or death due to any cause. Patients who are alive and progression-free will be censored on the date of their last disease assessment. Patients who receive subsequent treatment for myeloma before disease progression will be censored on the date of their last disease assessment prior to initiation of the subsequent treatment. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.(25)

16.323 Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier.

16.324 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.4 Data & Safety Monitoring

16.41 Safety review

The principal investigator(s) and the study statistician will review the study monthly 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 biannually, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rules

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 one of the following:

- If 5 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- If after the first 15 patients have been treated, 30% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 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.

16.5 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time all patients registered have either achieved a response (PR or better noted as the objective status on two consecutive evaluations) or have discontinued study treatment without achieving a response.

16.6 Subset Analyses for Minorities

16.61 Study availability

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

16.62 Statistical analysis by subset

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 analyses will look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 Regional population

The geographical region served by MCCC has a population which includes approximately 3% minorities. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	16	24	40
Ethnic Category: Total of all subjects	**16**	**25**	**41**
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	15	24	39
Racial Category: Total of all subjects	**16**	**25**	**41**

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. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

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

None.

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

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 insuring 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 prior to study entry as well as for evidence of response to study therapy and progression after study therapy. 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 progression of disease prior to study entry, supporting documentation includes the evidence needed to determine the patient's progression 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 insuring 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 is available on the Cancer Center Systems homepage.

19.0 Budget

19.1 Costs charged to patient: routine clinical care and cost of study drugs

19.3 Other budget concerns:

The Department of Hematology and Oncology at Mayo Clinic Florida will provide 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.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

Appendix II Creatinine Clearance (CrCl) Calculation

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

Appendix III New York Heart Association Classification of Congestive Heart Failure

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.
Original source: Criteria Committee, New York Heart Association , Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

Appendix IV Mayo Risk Stratification

High Risk

FISH deletion 17p

FISH t(14; 16)

FISH t(14; 20)

GEP (if done) High-risk signature

Intermediate Risk

FISH t(4:14)

Metaphase cytogenetic del 13

Hypodiploidy

Standard Risk

All others including:

FISH t(11; 14)

FISH t(6; 14)

Appendix V Patient Medication Diary

Name _____ **Study ID Number** _____

Please complete this diary on a daily basis. Write in the amount of the dose of pomalidomide and dexamethasone that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time; unless the dose was forgotten and remembered on the same day, in which case the dose can be taken that day.. Pomalidomide should be taken without food (at least 2 hours before or 2 hours after a meal). Do not open or crush capsules. Doses that are considered to be vomited are not to be made up and a mention about the time of dose and time of vomiting episode should be made in the pill diary.

If you experience any health/medical complaints or take any medication other than pomalidomide and dexamethasone, please record this information.

Study Drug(s)	**Dose**	**Study Coordinator only:** Write in the dose assigned by the study doctor in this column if different than the dose listed in the previous column
Pomalidomide	4 mg	
Dexamethasone	40 mg	

Week of: _____

	Day 1	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***
Date							
Pomalidomide							
Dexamethasone							

Week of: _____

	Day 8	***Day 9***	***Day 10***	***Day 11***	***Day 12***	***Day 13***	***Day 14***
Date							
Pomalidomide							
Dexamethasone							

Week of: _____

	Day 15	***Day 16***	***Day 17***	***Day 18***	***Day 19***	***Day 20***	***Day 21***
Date							
Pomalidomide							
Dexamethasone							

Week of: _____

	Day 22	***Day 23***	***Day 24***	***Day 25***	***Day 26***	***Day 27***	***Day 28***
Date							

Pomalidomide							
Dexamethasone							

Patient signature: _____

Health or medical complaints during this time:

Other medications or supplements taken during this time:

Name of medication or supplement	How much did you take? (example: Two 500mg pills)	When did you take it (examples: Every day Or Day 19 and Day 20)

Use a separate sheet of paper if more space is needed.

My next scheduled visit is: _____

If you have any questions, please call: _____

Study Coordinator Use Only

Number of pills returned _____ Number of vials returned: _____

Discrepancy Yes____/No____ Verified by _____ Date_____

Appendix VI Child Pugh Classification

Parameter	1 point	2 points	3 points
Total Bilirubin	<34 µmol/L (<2mg/dL)	34–50 µmol/L (2-3mg/dL)	>50 µmol/L (>3mg/dL)
Albumin Serum	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
Prothrombin Time	<1.7 (INR)	1.71-2.30 (INR)	>2.30 (INR)
Ascites	absent	Slight (medically controlled)	Moderate to Severe (poorly controlled)
Hepatic Encephalopathy*	None	Grade 1-2 (or suppressed with medication)	Grade 3-4 (or refractory)

***Grades of Hepatic Encephalopathy**

Grade 1 – Inverted sleep pattern; forgetfulness, agitation, irritability, apraxia

Grade 2 – Lethargy; disorientation for time or place, subtle personality change; asterixis, ataxia

Grade 3 – Somnolence but rousability; disorientation as regards place; asterixis, hyperactive reflexes, Babinski signs, muscle rigidity

Grade 4 – Coma (unresponsive to verbal or noxious stimuli)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. *The liver and portal hypertension.* Philadelphia: Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R. “Transection of the oesophagus for bleeding oesophageal varices”. *The British journal of surgery*, 1973; 60: 646-9.