A Phase II Study of Elotuzumab, Pomalidomide, & Dexamethasone (Elo-Pom-Dex) with Second Autologous Stem Cell Transplantation for Relapsed Multiple Myeloma

Washington University School of Medicine
Division of Oncology
660 South Euclid Avenue, Campus Box 8007
St. Louis, MO 63110

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Principal Investigator: **Ravi Vij, M.D.**
Phone: (314) 454-8323
E-mail: rvij@wustl.edu

Sub-Investigators:	**Institution:**	**Modality**
Christine Chen, M.D.	Princess Margaret Cancer Centre	Medical Oncology
Jeffrey Matous, M.D.	Sarah Cannon Research Institute	Medical Oncology
Ajay Nooka, M.D.	Emory Winship Cancer Institute	Medical Oncology
Feng Gao, Ph.D.	Washington University	Biostatistics

Study Drug(s): elotuzumab (Empliciti)
pomalidomide (Pomalyst)
dexamethasone (Decadron)

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CONFIDENTIAL

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Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

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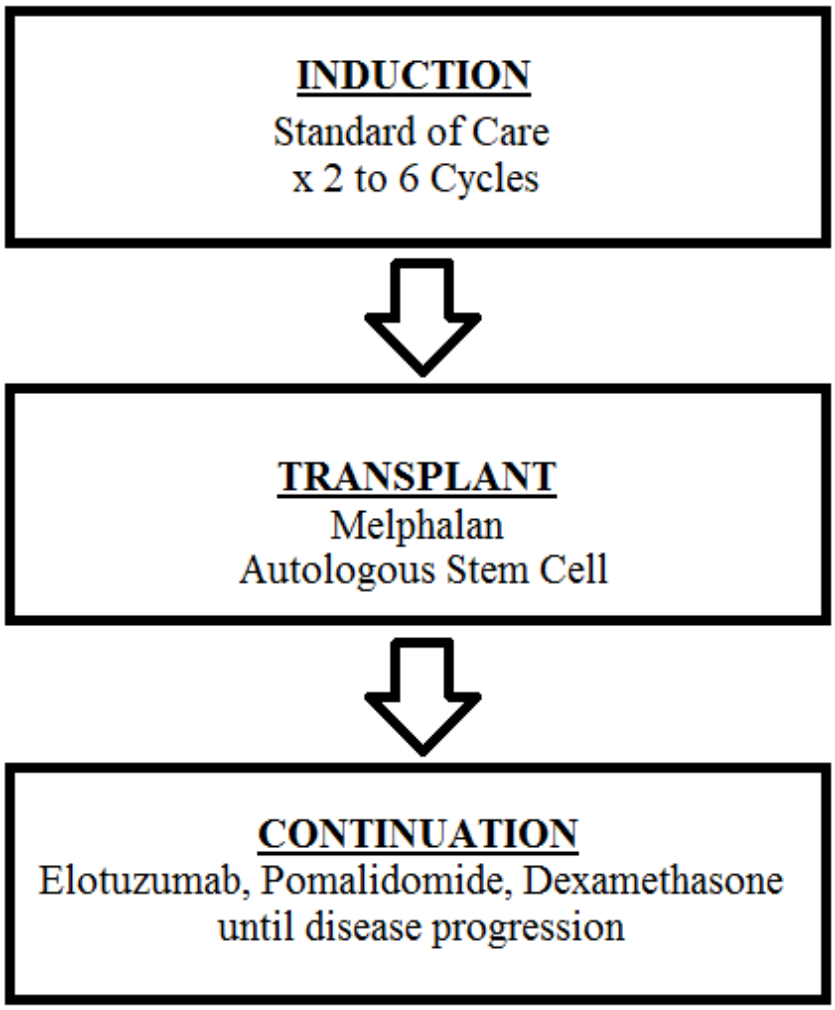
SCHEMA



Glossary of Abbreviations

AE	Adverse event
ALT(SGPT)	Alanine aminotransferase
ASCT	Autologous stem cell transplant
AST(SGOT)	Aspartate aminotransferase
BMS	Bristol-Myers Squibb
C	Celsius
CBC	Complete blood count
CMP	Comprehensive metabolic panel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRR	Complete remission rates
CT	Computerized tomography
D5W	Dextrose 5% water
dL	Deciliter
DOB	Date of birth
DSMC	Data and safety monitoring committee
EE	Efficacy-evaluable
EFS	Event-free survival
Elo-Pom-Dex or EPd	Elotuzumab, pomalidomide, and dexamethasone
EOS	End of study
FCBP	Female of childbearing potential
FNCBP	Female not of childbearing potential
FDA	Food and Drug Administration
H&P	History and phsycial
HRPO	Human Research Protection Office at Washington University
IB	Investigator's brochure
IEC	Institutional ethics committee
IMIDs	Immunomodulatory imide drugs
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
KG	Kilogram
L	Liter
MG	Milligram
min	Minute
mL	Milliliter
MM	Multiple myeloma
µmol	Millimole
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease

PET	Positron emission tomography
PFS	Progression-free survival
PPP	Pregnancy prevention plan
PR	Partial response
PS	Performance status
QASMC	Quality Assurance and Safety Monitoring Committee
SAE	Serious adverse event
sCR	Stringent complete response
SD	Stable disease
SPEP	Serum protein electrophoresis
SWFI	Sterile Water for Injection
UPEP	Urine protein electrophoresis
UPN	Unique patient number
VGPR	Very good partial response
VTE	Venous thromboembolism
WUSM	Washington University School of Medicine

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1.0 BACKGROUND AND RATIONALE

1.1 Multiple Myeloma

Multiple myeloma (MM) is a multifocal plasma cell neoplasm resulting from the clonal expansion of terminally differentiated B-cells. The disease is characterized by a serum or urine monoclonal protein and skeletal destruction with osteolytic lesions, bone pain, pathologic fractures, and hypercalcemia. Recurrent infections from depressed normal immunoglobulin production, renal dysfunction from light chain production, and anemia from generalized marrow involvement are also common. MM is the second most common hematological malignancy in the United States, accounting for more than 22,000 new cases and over 10,500 deaths in 2013. [1]

1.2 Autologous Stem Cell Transplant

Treatment with high-dose chemotherapy and autologous stem cell transplant (ASCT) results in improved overall response rates (ORRs), complete remission (CR) rates, and progression-free survival (PFS) and overall survival (OS) compared with treatment with standard dose chemotherapy. [2] Recent studies have shown that lenalidomide maintenance therapy after ASCT further prolongs PFS. [3, 4] Despite the benefits of ASCT and lenalidomide maintenance, MM remains incurable, with the median PFS after ASCT of 41–46 months. [3, 4]

For patients who relapse after ASCT, a second ASCT was historically a common salvage therapy. Second ASCT does improve PFS and OS compared to conventional salvage therapy [5, 6]. However, the PFS following second ASCT is limited and is generally less than 50% compared with that of the first ASCT. [7-11] In patients who fail ASCT with lenalidomide maintenance, the PFS following second ASCT are even more modest. We retrospectively reviewed 20 patients treated with second ASCT after initial ASCT with lenalidomide maintenance. The estimated median PFS was 13 months following second ASCT compared to 36 months following initial ASCT despite nearly all patients receiving maintenance therapy following second ASCT (unpublished data).

Recent studies have looked to improve the outcomes following second ASCT using more intensive conditioning regimens, but none have yet shown improvement in response rate, PFS, or OS. [12-19] It is currently unknown if maintenance/continuation therapy following second ASCT will results in similar PFS gains as it does following initial ASCT. At the time of second ASCT, most patients have already failed proteasome inhibitors and immunomodulatory imide drugs (IMIDs) and thus novel regimens are needed for this indication.

1.3 Elotuzumab

Elotuzumab (Empliciti; BMS-901608; HuLuc63) is a humanized recombinant monoclonal IgG1 antibody product directed to human SLAMF7 (also known as CRACC and CS1), a cell surface glycoprotein highly expressed in myeloma cells. When added to lenalidomide and dexamethasone, elotuzumab is well tolerated and has been shown to increase response rates, PFS, and OS in patients with relapsed MM. Based on this, elotuzumab received FDA approval for this indication. However, the utility of the regimen is somewhat limited as many relapsed patients have previously failed lenalidomide, and in such patients, response is modest. Numerous clinical trials are currently ongoing utilizing elotuzumab in different regimens and different indications, such as continuation therapy.

1.4 Pomalidomide

Pomalidomide, a second generation thalidomide analog with immunomodulatory properties like lenalidomide, was recently approved in combination with dexamethasone for use in subjects with refractory or relapsed and refractory MM who have failed bortezomib and lenalidomide.

As lenalidomide and pomalidomide are in the same class of drugs and have a similar safety and pharmacokinetic profile, elotuzumab is expected to elicit a similar safety profile in combination with pomalidomide as it does in combination with lenalidomide. In addition, the combination may elicit response in patients later in the disease course as pomalidomide is active against lenalidomide resistant MM cells. The combination of elotuzumab, pomalidomide, and dexamethasone (Elo-Pom-Dex or EPd) is currently being evaluated by a number of clinical trials in the relapsed/refractory setting (clinicaltrials.gov NCT02612779, NCT02718833, NCT02654132, and NCT02726581).

1.5 Study Rationale

Based on the need to improve outcomes post second ASCT for MM and the benefits seen of maintenance treatment following initial ASCT, the natural next step is to evaluate maintenance/continuation therapy following second ASCT.

Pomalidomide is active against MM cells refractory to both bortezomib and lenalidomide, making it an ideal choice for continuation therapy following second ASCT. Adding elotuzumab may increase efficacy and also the durability of responses which is essential to improving outcomes following second ASCT.

1.6 Correlative Studies Rationale

Samples will be collected for currently undefined future analyses.

2.0 OBJECTIVES

2.1 Primary Objective

To evaluate the one-year event-free survival (EFS) rate of patients with relapsed/refractory multiple myeloma following second ASCT with Elo-Pom-Dex continuation therapy.

2.2 Secondary Objectives

1. To evaluate the overall response rate (ORR) of patients with relapsed/refractory multiple myeloma following second ASCT with Elo-Pom-Dex continuation therapy
2. To evaluate the complete response rate (CRR) of patients with relapsed/refractory multiple myeloma following second ASCT with Elo-Pom-Dex continuation therapy
3. To evaluate the event-free survival (EFS) of patients with relapsed/refractory multiple myeloma following second ASCT with Elo-Pom-Dex continuation therapy
4. To evaluate the progression-free survival (PFS) of patients with relapsed/refractory multiple myeloma following second ASCT with Elo-Pom-Dex continuation therapy
5. To evaluate the overall survival (OS) of patients with relapsed/refractory multiple myeloma following second ASCT with Elo-Pom-Dex continuation therapy.
6. To evaluate the toxicity of second ASCT with Elo-Pom-Dex continuation therapy.

2.3 Exploratory Objectives

1. To evaluate the minimal residual disease negative (MRD-negative) rate of patients with relapsed/refractory multiple myeloma following second ASCT with Elo-Pom-Dex continuation therapy
2. To compare the outcomes of patients with relapsed/refractory multiple myeloma following second ASCT with Elo-Pom-Dex continuation therapy with a similar cohort of patients treated with alternative therapies off-study.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically confirmed diagnosis of multiple myeloma.

2. Received prior autologous stem cell transplantation as first line therapy for multiple myeloma with subsequent disease relapse/progression.

3. Failed 1 or 2 prior lines of treatment for multiple myeloma. A line of treatment includes all therapy including induction, transplant, and maintenance administered in a sequence in the absence of relapse/progression. Once relapse/progression occurs and subsequently the anti-myeloma treatment is changed, a new line of treatment has begun. Local radiation or corticosteroids will not be considered treatment for multiple myeloma.

4. Received 2 to 6 cycles of induction therapy per standard of care prior to 2nd autologous stem cell transplantation.

5. Received standard of care melphalan conditioning for 2nd autologous stem cell transplantation, is currently Day +80 to +120 following transplant, and is responding to therapy (partial response or better as compared to pre-induction assessment; see section 10.0 for response definitions).

6. All US 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. For Canadian sites, patients will followed according to the Pomalidomide pregnancy prevention program (Appendix E).

7. Females of reproductive potential within the US must agree to adhere to the scheduled pregnancy testing as required in the POMALYST REMS® program. For Canadian sites, patients will followed according to the Pomalidomide pregnancy prevention program (Appendix E).

8. At least 18 and no more than 75 years of age at enrollment.

9. ECOG performance status ≤ 2 (Appendix A).

10. Normal bone marrow and organ function as defined as ALL of the following:
    a. Absolute neutrophil count ≥ 1000/mm3
    b. Platelets ≥ 75,000/mm3 (transfusions not permitted within 7 days of screening)
    c. Total bilirubin ≤ 2.0 x IULN
    d. AST(SGOT)/ALT(SGPT) ≤ 3.0 x IULN
    e. Creatinine clearance (Appendix B) ≥ 15 mL/min

11. Females of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry through Day +100 visit. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

12. Able to understand and willing to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

1. Refractory to elotuzumab and/or pomalidomide, defined as progressive disease or clinical relapse on therapy or within 60 days following completion of therapy (see section 10.0 for response definitions). Prior exposure to elotuzumab and/or pomalidomide is allowed as long as patient is not refractory to these agents.

2. More than one prior transplant prior to study entry with the exception of tandem

transplantation. Tandem transplantation is defined as two autologous stem cell transplants that occur within 9 months of one another, and the patient did not have disease progression in the period between the two transplants.

3. Presence of peripheral neuropathy ≥ grade 3 based on NCI CTCAE v 4.0

4. History of plasma cell leukemia or MM CNS involvement.

5. Receiving renal replacement therapy, hemodialysis, or peritoneal dialysis.

6. Diagnosed with another concurrent malignancy requiring treatment.

7. Known HIV or active hepatitis A, B, or C. Antibody testing not required for screening.

8. Known hypersensitivity to pomalidomide, dexamethasone, or any excipients in elotuzumab, formulation, or recombinant protein

9. Receiving any other investigational agents within 14 days prior to enrollment.

10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

11. Pregnant and/or breastfeeding. Females of childbearing potential must have **two** negative pregnancy tests. The first test should be performed within 10-14 days of study entry, and the second test within 24 hours prior to prescribing pomalidomide.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

3.4 Retrospective Cohort

As the data on second ASCT is scant in the modern therapy era, a cohort of patients meeting the eligibility criteria above who underwent second ASCT at the institution 11/22/2017-10/01/2021 (to mirror enrollment period for the prospective trial) and did not enroll on the prospective trial of Elo-Pom-Dex continuation will be recruited. The retrospective data is being used to provide context to the clinical trial data. Based on the number of second ASCTs performed among patients not enrolled on this trial, we estimate ~30-40 records will be reviewed and ~20 will be eligible for the analysis.

For those meeting eligibility, similar data will be collected as outlined in section 9.0, with the exception of adverse events and continuation forms. Adverse events will not be collected. Granular data on continuation treatment will not be collected each cycle, rather the start and stop dates and response data will be collected for the regimen(s) administered.

4.0 REGISTRATION PROCEDURES

In general, patients will sign informed consent prior to 2nd autologous transplantation. However, patients may be allowed to consent following 2nd autologous transplantation with permission from the principal investigator. Patients will undergo screening and registration following 2nd autologous stem cell transplantation. Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center. Patients on the retrospective arm of the study will not be formally registered.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Overview

Patients will have received 2 to 6 cycle of salvage/induction per standard of care. Following induction, patients will undergo standard of care ASCT melphalan conditioning. Administration of melphalan and the second ASCT will be done as part of routine care and procedures are not dictated by this protocol.

Continuation therapy with Elo-Pom-Dex will begin between Days 80 and 120 following the second ASCT for patients meeting protocol eligibility. Barring dose modifications, Elo-Pom-Dex continuation therapy will consist of

- 10 mg/kg of elotuzumab on Days 1 and 15 for Cycles 1-6 followed by 20 mg/kg on Day 1 for Cycles 7+
- 2 mg of pomalidomide daily on Days 1-21 of all cycles
- 40 mg of dexamethasone on Days 1 and 15 for Cycles 1-6 followed by 40 mg on Day 1 for Cycles 7+

Continuation therapy may continue until relapse or progression.

5.2 Elotuzumab Administration

During continuation therapy, elotuzumab will be administered on a 28-day cycle as follows: on Days 1 and 15 for Cycles 1-6 and on Day 1 for Cycles 7+. For Cycles 1-6 elotuzumab will be administered intravenously at a dose of 10 mg/kg. For Cycles 7+ elotuzumab will be administered at a dose of 20 mg/kg.

As per standard elotuzumab treatment guidelines, patients must be premedicated 45-90 minutes prior with the following:

- H1 blocker: diphenhydramine (25-50 mg PO or IV) or equivalent
- H2 blocker: ranitidine (50 mg PO or IV) or equivalent
- Acetaminophen (650-1000 mg PO)
- Dexamethasone (8 mg IV) (PO dosing will be reduced to accommodate IV premedication for elotuzumab)

During the first cycle of continuation and escalation to 20mg/kg (Cycle 7 of continuation) the elotuzumab infusion rate will be increased gradually to a maximum of 5mL/min. See Appendix C for elotuzumab preparation and administration guidelines.

On each day of elotuzumab, vital signs monitoring should be performed at the following time points:

- prior to the start of the elotuzumab infusion
- 30 minutes after the start of infusion
- at the end of the infusion
- 30 minutes post completion of infusion

Patients should be monitored for toxicity and doses of elotuzumab should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment or dose interruptions (see Section 6.0). No elotuzumab dose reductions are allowed.

5.3 Pomalidomide Administration

During continuation therapy, pomalidomide will be taken by mouth daily on Days 1-21 of each 28-day cycle at a starting dose of 2 mg. During continuation, pomalidomide may be dose escalated to 4 mg at the discretion of the treating physician.

Pomalidomide (POMALYST®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. For US patients, pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS® program. Per the standard POMALYST REMS® program requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS® program.

For Canadian sites, pomalidomide will be supplied as Investigational Product by Celgene Corporation.

Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle. This is in accordance with the POMALYST REMS® program.

VTE prophylaxis with aspirin 81 mg daily should be administered unless the patient is being treated with alternate prophylaxis (Coumadin, low molecular weight heparin, etc) or VTE prophylaxis is contraindicated.

Females must follow pregnancy testing requirements as outlined in the POMALYST REMS® program (US) or Appendix E (Canada).

Patients should be monitored for toxicity and doses of pomalidomide should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of pomalidomide dose (see Section 6.0). Once pomalidomide is reduced for toxicity, no dose re-escalation is permitted.

Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal.

Pomalidomide should be taken at the same time each day. On days when both pomalidomide and elotuzumab are being administered, pomalidomide should be taken at least 2 hours following the end of the elotuzumab infusion. 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, rather it should be taken at the next scheduled time point. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose. 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.

5.4 Dexamethasone Administration

During continuation therapy, dexamethasone will be taken by mouth at a starting dose of 40 mg. It will be given on a 28-day cycle as follows: on Days 1 and 15 for Cycles 1-6 and on Day 1 only for Cycles 7+. Sufficient quantity of drug for one cycle of therapy will be prescribed to the patient at a time.

NOTE: On elotuzumab dosing days, patients will receive IV premedication with dexamethasone 8 mg prior to administration of elotuzumab, so the PO dosing will be reduced to 28 mg, to be taken 3-24 hours prior to elotuzumab infusion.

Patients should be monitored for toxicity and doses of dexamethasone should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of dexamethasone dose (see Section 6.0). Once dexamethasone is reduced for toxicity, no dose re-escalation is permitted.

Dexamethasone should be taken with food or milk. Patients should be instructed to swallow dexamethasone tablets whole and not to break, chew, or open the tablets. Each tablet should be swallowed separately with a sip of water.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 8 hours or more away. A double dose should not be taken to make up for a missed dose. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

5.5 Melphalan Conditioning and Stem Cell Transplantation

Melphalan conditioning prior to ASCT will be administered according to institutional guidelines. Recommendations for melphalan dosing are that it be given 200mg/m^2 on Day -2 pre-ASCT, with possible dose reduction to 140mg/m^2 due to advanced age or other contraindication.

Autologous peripheral blood stem cells (at least $2x10^6$ $CD34^+$ cells/kg recommended) will be given on Day 0 to all patients according to institutional guidelines.

5.6 General Concomitant Medication and Supportive Care Guidelines

5.6.1 Prohibited Concomitant Medications and Procedures

The following procedures are prohibited during the study.

- Any antineoplastic treatment with activity against MM other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)
- Co-administration of strong inhibitors of CYP1A2 (unless medically necessary). Co-administration of pomalidomide with drugs that are strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin, and fluvoxamine) and CYP3A4/5 (e.g. ketoconazole) or P-gp could increase pomalidomide exposure and should be avoided, unless medically necessary.

5.6.2 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted, but should not be given prophylactically. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the principal investigator.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Antiviral therapy such as acyclovir may be administered if medically appropriate.
- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery, have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

5.7 Females of Childbearing Potential

Female of childbearing potential (FCBP) is defined as a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the

surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months). FBCP are required to have **two** negative serum pregnancy tests prior to the first dose of continuation therapy because pomalidomide is a thalidomide analogue and is contraindicated for use during pregnancy, as thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. Of the two negative pregnancy tests required prior to initiating therapy, the first should be performed within 10-14 days and the second within 24 hours prior to prescribing pomalidomide.

In addition, FCBP should undergo weekly pregnancy tests during the first cycle of continuation and on Day 1 of each cycle thereafter for women with regular menstrual cycles or on Days 1 and 15 of each cycle thereafter for women with irregular menstrual cycles.

Female patients are required either to abstain continuously from heterosexual sexual intercourse or to use acceptable contraception, beginning 4 weeks prior to initiating treatment with pomalidomide, during therapy, during dose interruptions (including the post-ASCT period), and continuing for 4 weeks following discontinuation of pomalidomide. Acceptable contraception is defined as two methods of reliable birth control simultaneously: one highly effective form of contraception (tubal ligation, IUD, hormonal [pills, injections, hormonal patches, vaginal rings, or implants], or partner's vasectomy) and one additional effective form of contraception (male latex or synthetic condom, diaphragm, or cervical cap).

Male patients must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking pomalidomide and for 4 weeks following discontinuation of pomalidomide, even if they have undergone a successful vasectomy. Male patients taking pomalidomide must not donate sperm.

5.8 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms. Otherwise, therapy may continue for an indefinite number of cycles of continuation therapy.

Patients will be removed from the study for any of the following reasons:

- Disease progression or relapse
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy

- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

If a patient is withdrawn from study, the sponsor should be notified as soon as possible. Patients who are removed from study will undergo an end of study visit (see section 7.0) then will enter into the follow-up phase of the trial. Patients who withdraw will not be replaced.

5.9 Duration of Follow-up

Participants will be followed annually for progression-free and overall survival for up to 5 years after removal from study or until death, whichever occurs first. Follow-up can include an office visit and a physical exam, or a phone call from a study coordinator or research nurse to the patient.

6.0 DOSE MODIFICATIONS

Elotuzumab, pomalidomide, and dexamethasone dosing is independent. If a patient discontinues either elotuzumab or pomalidomide, the patient may continue on study receiving the other treatments. Toxicities should be attributed to a specific study drug if possible so that dose modifications can be made rationally. If multiple toxicities are noted, the dose adjustments and or/delays should made once per cycle according to the guidelines for the most severe toxicity. The maximum delay allowed before treatment must be discontinued will be 3 weeks unless permission to resume treatment is granted by the principal investigator. Alternative dose modifications than those listed below may be recommended after discussion with the principal investigator in order to maximize exposure to study treatment while protecting patient safety.

6.1 Dose Levels

Elotuzumab Dose Levels

Dose Level	Dose (mg)
Starting Dose	10 mg/kg
-1	Discontinue (no dose modifications allowed)

Pomalidomide Dose Levels

Dose Level	Dose (mg)
Starting Dose	4 mg
-1	3 mg
-2	2 mg
-3	1 mg
-4	Discontinue

Dexamethasone Dose Levels

Dose Level	Dose (mg)
Starting Dose	40 mg[1]
-1	20 mg[2]
-2	12 mg[3]
-3	Discontinue

1- 28 mg orally and 8 mg intravenously on elotuzumab dosing days
2- 8 mg orally and 8 mg intravenously on elotuzumab dosing days
3- 0 mg orally and 8 mg intravenously on elotuzumab dosing days

6.2 Dosing Modifications for Hematologic Toxicities

6.2.1 Thrombocytopenia

Only thrombocytopenia determined to be related to one or more study drugs requires dose reductions or adjustments as described in this section. Platelet transfusion support is permissible at the discretion of the treating physician. Participants who have treatment delayed for greater than three weeks should discontinue protocol therapy.

Dose modifications for thrombocytopenia should be instituted as follows:

Platelet Count	Grade	Modification		
		Elotuzumab	Pomalidomide	Dexamethasone
< 25,000/mm^3	4	No changes.	**Each episode:** Hold until platelets resolve to grade ≤ 1, then reduce by one dose level	No changes.

6.2.2 Neutropenia or Febrile Neutropenia

Only neutropenia/febrile neutropenia determined to be related to one or more study drugs requires dose reductions or adjustments as described in this section. Colony-stimulating factor support (such as G-CSF or GM-CSF) for neutropenia is permissible at the discretion of the treating physician, but should not be given prophylactically. Participants who have treatment delayed for greater than three weeks should discontinue protocol therapy.

Dose modifications for neutropenia should be instituted as follows:

Neutrophil Count	Grade	Modification		
		Elotuzumab	Pomalidomide	Dexamethasone
< 500/mm^3	4	No changes.	**Each episode:** Hold until neutrophils resolve to grade ≤ 1, then reduce by one dose level	No changes.

6.3 Dosing Modifications for Non-Hematologic Toxicities

Dose modification guidelines for treatment related non-hematologic toxicities are as follows:

Toxicity	Grade	Modification		
		Elotuzumab	Pomalidomide	Dexamethasone
Confusion or Mood Alteration	2 or 3	No changes		**First episode:** Hold until symptoms resolve to baseline, then reduce by one dose level. **Second episode:** Discontinue dexamethasone
	4			**First episode:** Discontinue dexamethasone
Diarrhea	3	**Each episode:** Only if the event occurred despite optimal supportive therapy, hold suspected study drug(s) until toxicity resolves to ≤ grade 1 or baseline, then reduce suspected drug(s) by one dose level.		
	4	**Each episode:** Discontinue suspected study drug(s).		
Dyspepsia, Gastric or duodenal ulcer, or Gastritis	2	No changes.		**Each episode:** Treat with histamine-2 blockers, sucralfate, or omeprazole as needed. If symptoms persist despite these measures, decrease dexamethasone by 1 dose level.
	3			**First episode:** Hold until toxicity resolves to ≤ grade 1 or baseline, then decrease dexamethasone by 1 dose level. Prophylactically treat with histamine-2 blockers, sucralfate, or omeprazole as needed. **Second episode:** If symptoms persist despite these measures, discontinue dexamethasone.

Toxicity	Grade	Modification		
		Elotuzumab	Pomalidomide	Dexamethasone
Edema	3	No changes.		**First episode:** Treat with diuretics as needed. Decrease dexamethasone by one dose level. **Second episode:** If edema persists, decrease dexamethasone by one more dose level. **Third episode:** Discontinue dexamethasone
Elotuzumab Infusion Reaction	1	No changes.		**No changes.**
	2 or 3	First episode: Interrupt infusion if applicable. See Appendix D for instructions. Second episode: Discontinue elotuzumab.		
	4	First episode: Discontinue elotuzumab.		
Fatigue	Any	No Changes		
Hyperglycemia	3	No changes.		**Each episode:** Treat with insulin or hypoglycemic as needed. If uncontrolled despite these measures, decrease dexamethasone by 1 dose level.
	4			**First episode:** Discontinue dexamethasone.

Toxicity	Grade	Modification		
		Elotuzumab	Pomalidomide	Dexamethasone
Muscle Weakness	2 or 3	No changes.		**First episode:** Decrease dexamethasone by one dose level. **Second episode:** If weakness persists, decrease dexamethasone by one more dose level. **Third episode:** Discontinue dexamethasone.
Nausea/Vomiting	3	**Each episode:** Only if the event occurred despite optimal anti-emetic prophylaxis, hold suspected study drug(s) until toxicity resolves to ≤ grade 1 or baseline, then reduce suspected drug(s) by one dose level.		
Pancreatitis	2 - 4	No changes.		**First episode:** Discontinue dexamethasone.
Peripheral Neuropathy	2 with pain	No changes.	**Each episode:** Hold until toxicity resolves to ≤ grade 1 or baseline, then reduce by one dose level.	No changes.
	3 or 4		**Each episode:** Hold until toxicity resolves to ≤ grade 1 or baseline, then reduce by one dose level.	
Rash	2 or 3	**Each episode:** Hold suspected study drug(s) until toxicity resolves to ≤ grade 1 or baseline, then restart at previous dose level or reduce by one dose level at the investigator's discretion		
	4	**First episode:** Discontinue suspected study drug(s).		

Toxicity	Grade	Modification		
		Elotuzumab	Pomalidomide	Dexamethasone
Thrombosis or Embolism	2 or 3	No changes.	**Each episode:** Hold pomalidomide and commence anticoagulation therapy, then restart at previous dose level at the investigator's discretion.	No changes.
	4	**Each episode:** Discontinue suspected study drug(s).		
Tumor Lysis Syndrome	Any	**First episode:** Hold **all** drugs until symptoms resolve to baseline, then restart at previous dose levels with appropriate TLS prophylaxis **Second episode:** Discontinue protocol treatment.		
Other non-hematologic toxicity	3	**Each episode:** Hold suspected study drug(s) until toxicity resolves to ≤ grade 1 or baseline, then reduce suspected drug(s) by one dose level.		
	4	**Each episode:** Discontinue suspected study drug(s).		

7.0 STUDY CALENDAR

	Pre-ASCT Screening[1]	ASCT[2]	Post-ASCT Screening[3]	Continuation[4]		EOS[5]
				D1	D15[16]	
Informed consent	X					
H&P w/ PS & plasmacytoma assessment	X		X	X[14]		X
CBC	X		X	X[14]	X[16]	X
CMP[6]	X			X[14]		
SPEP	X		X	X[14]		X
Serum Immunofixation	X		X	X[15]		
24h urine for total protein, and UPEP [7]	X		X	X[14]		X
Urine Immunofixation[7]	X		X	X[15]		
Serum-free light chains	X		X	X[14]		X
Quantitative immunoglobulins (IgA, IgG, IgM)	X		X	X[14]		X
Serum βhCG[8]			X	X	X[17]	X
Bone marrow biopsy and aspirate[9]	X		X	X[15]		
Skeletal imaging[10]	As clinically indicated					
Elotuzumab[11]				X	X[16]	
Pomalidomide				Days 1-21		
Dexamethasone				X	X[16]	
Melphalan ASCT		X				
Blood for future research[12]	X		X	X[15]		
Bone marrow aspirate for research	X		X	X[15]		
Adverse event monitoring				X ---------- X		

Note- A window of -7 to +7 is allowed during continuation therapy cycles.

1. Within 60 days prior to ASCT. For patients who sign consent following ASCT, any missed assessments will not be counted as protocol deviations.
2. As according to institutional guidelines.
3. Day +80 to Day +120 post-ASCT; to occur within 28 days prior to C1D1 of continuation therapy.
4. First cycle of continuation therapy must begin between Days +80 to +120 post-ASCT and may continue until disease progression or unacceptable toxicity
5. Within 30 days of last dose of study drugs; following EOS patients will be followed annually for PFS and OS for up to 5 years.
6. Includes electrolytes, renal function, protein, and liver function tests
7. Repeat 24h urine only required for patients with ≥ 200 mg/24h of M-protein at screening
8. Females of childbearing potential only
9. Bone marrow aspirate and core biopsy – differential required; Cytogenetics, and fluorescent *in situ* hybridization (FISH) studies performed per institutional guidelines. MRD assessment should be performed for patients in VGPR/CR/sCR.
10. X-rays, CT, MRI, or PET per institutional guidelines
11. On elotuzumab dosing days, vital signs monitoring should be performed at the following time points: prior to the start of the elotuzumab infusion, thirty minutes after the start of infusion, at the end of the infusion, thirty minutes post completion of the elotuzumab infusion.
12. See Section 8.0 for details
13. Two negative tests are required before initiation of pomalidomide; one within 10-14 days prior and one 24 hours prior to prescribing.
14. Not required on C1D1 if screening/restaging visit occurred within 28 days prior
15. Cycle 13 only
16. Cycles 1-6 only
17. Required for all females of childbearing potential in Cycle 1; Only required beyond Cycle 1 for women with irregular menstrual cycles.

8.0 CENTRAL LABS

8.1 Future Research

Specimens from blood and marrow will be collected and stored for future research including, but not limited to, genetic studies.

Approximately 5 ml of bone marrow aspirate and 20 ml of peripheral blood in EDTA (pink top) tube(s) will be collected at the following time points:

- Pre-ASCT screening
- Post-ASCT screening
- Cycle 13 of continuation
- Time of MRD assessment(s)

Instructions for handling and shipment of central labs will be provided in the study lab binder.

9.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form Medical History Form Treatment History Form MM History MM Labs Form Extramedullary Disease Form	At Baseline
MM Labs Form	Screening and Each Cycle of Treatment
CBC Form	Screening and Each Cycle of Treatment
Central Labs Form	Screening and cycle 13 of continuation
MRD Form	Screening and cycle 13 of continuation
ASCT Form	At Baseline
Bone Marrow Form	Screening and cycle 13 of continuation

Continuation Form	Completion of each cycle of treatment
IMWG Response Form	Screening and cycle 13 of continuation
Adverse Events	Continuous from baseline through safety follow-up visit
MedWatch Form	See Section 11.0 for reporting requirements
SAE / CIOMS Form	See section 11.0 for reporting requirements for Canada
End of Treatment Form	At the completion of treatment
PD/Clinical Relapse Form	At the time of disease progression/clinical relapse
Follow-Up Form	Per protocol requirements
Death Form	At time of death

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

9.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 11.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

10.0 MEASUREMENT OF EFFECT

10.1 Response Criteria

Elotuzumab, a humanized IgG Kappa monoclonal antibody, can be detected in the serum by electrophoresis and/or immunofixation. Thus, its administration can interfere with the standard International Myeloma Working Group (IMWG) Uniform Response Criteria guidelines. Therefore, we will use a modified response criteria utilizing minimal residual disease detection by next-generation sequencing. [20-21]

10.1.1 Minimal Residual Disease

For patients in VGPR, CR, or sCR as defined below, minimal residual disease (MRD) testing should be performed using clonoSEQ next-generation sequencing technology [22]. Patients will be classified as MRD-negative or MRD-positive based on the current detection limits of the test (1 MM cell per $1x10^6$ cells).

Note: Anytime MRD assessment is performed, correlative studies should also be performed. See Section 9.0 for details.

10.1.2 Stringent Complete Response

Stringent complete response (sCR) requires all of the following:

- CR as defined below
- Normal free light chain ratio (0.26-1.65)
- Absence of clonal cells in the bone marrow by immunohistochemistry or immunofluorescence

10.1.3 Complete Response

Complete response (CR) requires all of the following:

- Disappearance of monoclonal protein by both protein electrophoresis and immunofixation studies from the blood and urine
- If serum and urine monoclonal protein are unmeasurable, Normal free light chain ratio (0.26-1.65)
- <5% plasma cells in the bone marrow
- Disappearance of soft tissue plasmacytoma

Patients who do not meet the definition of CR based solely on residual monoclonal protein on serum electrophoresis and/or immunofixation, but are MRD-negative as described above, will also be considered CR.

10.1.4 Very Good Partial Response

Very good partial response (VGPR) requires all of the following:

- Serum and urine monoclonal protein detectable by immunofixation but not on electrophoresis
  OR
  ≥ 90% reduction in serum monoclonal protein with urine monoclonal protein < 100 mg per 24 hours
- If serum and urine monoclonal protein are unmeasurable, a ≥ 90% decrease in difference between the involved and uninvolved free light chain levels is required in place of monoclonal protein criteria (The absolute decrease must be > 10 mg/dl)
- If present, > 50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examinations)

10.1.5 Partial Response

Partial response (PR) requires all of the following:

- ≥ 50% reduction in the level of the serum monoclonal protein
- Reduction in urine monoclonal protein by either ≥ 90% or to < 200 mg

- If serum and urine monoclonal protein are unmeasurable, a ≥50% decrease in difference between the involved and uninvolved free light chain levels is required in place of monoclonal protein criteria (The absolute decrease must be > 10 mg/dl)
- If serum and urine monoclonal protein are unmeasurable and serum free light chain is unmeasurable, a ≥ 50% reduction in plasma cells is required in place of monoclonal protein, provided that baseline bone marrow plasma cell percentage was ≥ 30%
- If present, > 50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examinations).

10.1.6 Stable Disease

Stable disease (SD) is defined as not meeting criteria for any other response as defined in this section.

10.1.7 Progressive Disease or Clinical Relapse

Progressive disease (PD) requires one or more of the following:

- ≥ 25% increase in the level of serum monoclonal protein, which must also be an absolute increase of at least 0.5 g/dL and confirmed on a repeat investigation
- ≥ 25% increase in 24-hour urine monoclonal protein, which must also be an absolute increase of at least 200 mg/24hr and confirmed on a repeat investigation.
- If serum and urine monoclonal protein are unmeasurable, ≥ 25% increase in the difference between involved and uninvolved free light chain levels, which must also be an absolute increase of at least 10 mg/dL and confirmed on a repeat investigation
- ≥ 25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%. As results may be inconsistent due to the heterogeneity of the bone marrow or sampling issues, patients with ≥ 25% increase in plasma cells may be allowed to continue on study at the discretion of the treating physician if the patient does not meet any of the other definitions of progressive disease. For response assessment, the marrow results will be disregarded in these cases.
- Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas. A definite increase is defined as at least 50% (and at least 1 cm) increase as measured serially as the sum of the products of the cross-diameters of the lesions.
- Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture).
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L not attributable to any cause other than progressive multiple myeloma).
- Decrease in hemoglobin > 2 g/dl not attributable to any cause other than

progressive multiple myeloma
- Increase in creatinine by > 2 mg/dl not attributable to any cause other than progressive multiple myeloma
- Other worsening laboratory result, or clinical condition that the treating physician determines is not attributable to any cause other than progressive multiple myeloma

Note: A response of progressive disease/clinical relapse nullifies any other concurrent response. For example, at a given time point that a participant meets criteria for VGPR but has development of new bone lesions, the response is PD not VGPR.

10.1.8 Relapse from Complete Response

Relapse from a complete response requires a prior CR or sCR as described above and subsequently developing one or more of the following:
- Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis excluding oligoclonal immune reconstitution, and confirmed on a repeat investigation
- Development of $\geq$ 5% plasma cells in the bone marrow aspirate or biopsy.
- Appearance of any sign of progressive disease or clinical relapse as stated above.

10.2 Event-Free Survival

Event-free survival (EFS) will be defined as time from ASCT to disease progression, relapse, or death, whichever occurs first. Patients who are removed from study therapy prior to any of these events occurring will be censored at the time of initiation of subsequent anti-myeloma treatment.

10.3 Progression-Free Survival

Progression-free survival (PFS) will be defined as time from ASCT to disease progression or relapse. Any patient who expires or withdraws prior to disease progression or relapse will be censored at last follow-up. Patients who are removed from study therapy prior to progression or relapse will be censored at the time of initiation of subsequent anti-myeloma treatment.

10.4 Overall Survival

Overall survival (OS) will be defined as time from ASCT to death due to any causes. Patients who are alive at the time of data analyses will be censored on the last known alive date. Patients who are removed from study therapy prior death will be censored at the time of initiation of subsequent anti-myeloma treatment.

10.5 Overall Response Rate

Overall response rate (ORR) will be defined as the proportion of evaluable patients meeting the criteria for PR, VGPR, CR, or sCR.

10.6 Complete Response Rate

Complete response rate (CRR) will be defined as the proportion of evaluable patients meeting the criteria CR or sCR.

11.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below. Please refer to Appendix BG for definitions and Appendix HC for a grid of reporting timelines.

Adverse events will be collected from first dose of study treatment through the end of study visit. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.
Refer to the data submission schedule in Section 101 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 11.01. Reporting requirements for secondary site study teams participating in Washington University-coordinated research may be found in Section 11.32.

11.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

11.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Washington University Sponsor Investigator or designee is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring

at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within 10 days of receipt of IRB acknowledgment via email to a QASMC auditorqasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

For events that occur at secondary sites, the Washington University Sponsor Investigator or designee is required to notify the QASMC within 10 days of Washington University notification via email to qasmc@wustl.edu. Submission to QASMC must include either the myIRB form and supporting documentation or (if not submitted to myIRB) the date of occurrence, description of the event, whether the event is described in the currently IRB approved materials, the event outcome, determination of relatedness, whether currently enrolled participants will be notified, and whether the informed consent document and/or any study procedures will be modified as a result of this event.

11.3 Secondary Sites Reporting Requirements

The research team at each secondary site is required to promptly notify the Washington University Sponsor-Investigator and designee and research coordinator of all serious adverse events (refer to Appendix GB, Section D) reportable events (as described in Section 7.6) within 1 working day of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA For 3500a (MedWatch) and Washington University's cover sheet (Appendix ID) form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University Sponsor-Investigator and designee and research coordinator within 10 working days4 calendar days (for fatal or life-threatening suspected adverse reactions) or 11 calendar days (for serious unexpected adverse reactions) of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within 1 working day of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA, and Millennium as needed.

Washington University pre-approval of all protocol exceptions must be obtained prior to implementing the change. Local IRB approval must be obtained as per local guidelines. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

11.4 Reporting to Secondary Sites

The Washington University Sponsor-Investigator (or designee) will notify the research team at each secondary site of all unanticipated problems involving risks to participants or others that have occurred at other sites within 10 working days of the occurrence of the event or notification of the Sponsor-Investigator(or designee) of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable. Refer to Section 16.0 (Multicenter Management) for more information.

11.5 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University principal investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix H for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix H) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix G) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
  - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

11.6 Reporting to Bristol-Myers Squibb

All serious adverse events (SAEs, defined in Section 11.1.2), unexpected adverse experiences (defined in Section 11.1.3), and life-threatening adverse events (defined in Section 11.1.4) that occur following study treatment commencement through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety regardless of relationship to study drug. Pregnancies must also be reported as an SAE.

Report within 24 hours to Worldwide.Safety@BMS.com or via facsimile at (609) 818-3804. If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within to BMS using the same procedure used for the initial SAE report. All SAEs should be followed to resolution or stabilization.

11.7 Reporting to Celgene

All serious adverse events (SAEs, defined in Section 11.1.2), unexpected adverse experiences (defined in Section 11.1.3), and life-threatening adverse events (defined in Section 11.1.4) that occur following study treatment commencement through 30 days of discontinuation of dosing must be reported to Celgene regardless of relationship to study drug. Pregnancies must also be reported as an SAE.

Report within 24 hours to drugsafety@celgene.com or via facsimile at (908) 673-9115 for US and (289)-291-4820 for Canada. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (PO-CL-MM-PI-008341) and the institutional protocol number should be

included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

All reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present.

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to pomalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.3 and Health Canada/ICH Guidance Document E2A: "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and Canadian Foods and Drugs Act C.05.014.

Participating study sites must report SAEs to Celgene as described and within 24 hours of awareness. Participating sites should also report SAEs to the primary study site.

Celgene Drug Safety Contact Information:
For US Study Sites:
Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Avenue, Summit, NJ 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

For Canadian Study Sites:
Celgene Inc.
6755 Mississauga Road,
Mississauga, ON
L5N 7Y2
Fax: (289) 291-4820
Email: drugsafety-canada@celgene.com

11.8 Timeframe for Reporting Required Events

Adverse events will be reported from study treatment commencement through 30 days of discontinuation of dosing or the start of next anti-myeloma therapy, whichever comes first.

11.9 Record Retention

As the sponsor, Washington University, will retain all source data and documentation pertaining to this clinical trial for a period of 25 years.

12.0 DATA AND SAFETY MONITORING

Board (DSMB) will be specifically convened for this trial to review toxicity data. A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

Until such a time as the first secondary site enrolls its first patient, a semi-annual DSM report to be prepared by the study team will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after study activation at Washington University (if at least one patient has been enrolled) or one year after study activation (if no patients have been enrolled at the six-month mark).

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the QASM Committee. The DSMB must meet at least every six months beginning six months after study activation at Washington beginning six months after enrollment of the first patient at a secondary site, no more than one month prior to the due date of the DSM report to QASMC.

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date and accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules

- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMC charter.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 11.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMB. This is located on the QASMC website at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

13.0 STATISTICAL CONSIDERATIONS

This is an open-label, single arm phase II study that will accrue at 5-6 centers within the United States. The total accrual goal is 40 patients evaluable for the primary objective. The estimated accrual is 1-2 patients per month, with a projected enrollment time frame of 24 months.

13.1 Determination of Sample Size

A power analysis was performed using one-sample log-rank test for the primary objective. The smallest increase in 1-year EFS rate with Elo-Pom-Dex continuation therapy is 20%, with a result of $\leq$ 19% being considered ineffective. Based on the literature, we estimate that the 1-year EFS following second melphalan ASCT is ~40%. Assuming EFS times follow an exponential distribution and a minimal 1-year follow-up period, forty evaluable patients will detect a 20% improvement (40% vs. 60%) in 1-year EFS with 80% power at 1-sided 0.05 alpha.

13.2 Data Analysis

Demographic and clinical characteristics of the sample, as well as adverse events, will be summarized using descriptive statistics. For continuous variables, the number of patients, mean, standard deviation, median, minimum and maximum will be provided. For categorical variables, the number and percent of patients in each demographic/characteristic category will be summarized.

All time-to-event variables (EFS, PFS, and OS) will be described using Kaplan-Meier product limit estimator. The 1 year EFS rate and its 90% confidence interval (CI) will be estimated using Kaplan-Meier product limit estimator. Kaplan-Meier curves will also be used to describe the association between response (both prior to and after continuation therapy) and EFS, PFS, and OS, and proportional hazards Cox models will be used to

control the potential confounding effects of other patient and clinical characteristics.

Response rates (MRD, ORR, CRR) will be described using descriptive statics with the corresponding 90% confidence intervals.

The final primary analysis will be performed once enrollment has been concluded and all treated patients have completed 1 year of follow-up post-ASCT and/or have been withdrawn from study treatment.

An interim analysis will be performed at the 2-year mark (where approximately one-half of patients will have at least 1-year follow-up if assuming uniform accrual) and the conditional power will be calculated for futility analysis based on the accumulated data. Conditional power is defined as the projected power to reject the null hypothesis at the end of the study given the data accrued up to the interim analysis. Therefore, a small value of conditional power indicates a highly likely, if not inevitable, conclusion of negative finding given the current data. If conditional power of 0.3 or less is obtained at the interim analysis, an early termination due to futility will be recommended.

Parallel analyses will be performed on the data of patients in retrospective cohort. As the data on second ASCT is scant in the modern therapy era, the retrospective data is being used to provide context to the clinical trial data. There will be no direct statistical comparisons between the prospective and retrospective cohorts.

13.3 Analysis Populations

13.3.1 Intent-to-Treat

The intent-to-treat (ITT) population will be defined as all patients who receive at least one dose of Elo-Pom-Dex continuation.

13.3.2 Safety

The safety population will be defined as all patients with at least one dose of Elo-Pom-Dex continuation.

13.4 Study Termination

There are no planned early stopping rules. However, at any time the study may be discontinued by the sponsor due to excessive toxicity, enrollment issues, etc. In this event, all participating sites, physicians, and patients will be notified and alternative treatment plans will be arranged.

14.0 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

15.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality

Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.

- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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APPENDIX A: ECOG Performance Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140\text{–age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[μmol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[μmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

APPENDIX C: Elotuzumab Preparation and Administration Guidelines

Product Description / Class and Dosage Form	Potency	IMP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Elotuzumab Powder for Solution for Infusion	400 mg or 300mg/vial	IMP	Open Label	20 mL Vial/ Sterile, white to off-white, preservative-free, lyophilized cake	Store at 2°C - 8°C

Dose Preparation Instructions

After dilution in normal saline, elotuzumab infusion must be completed within 8 hours if kept at room temperature (25C). In the United States and Puerto Rico, where a shortage of normal saline has been reported, dextrose 5% water (D5W) may be used. Normal saline is the preferred diluent and D5W should only be used if normal saline is not available. If a delay is anticipated after the dose has been diluted in normal saline, the prepared dose (properly identified) may be refrigerated at 2C to 8C for up to 24 hours. If stored under refrigerated conditions, the study drug solution should be equilibrated to room temperature (takes about 2 to 2.5 hours), and the container must be gently inverted to thoroughly mix the contents before administration. If the storage time limit is exceeded, the prepared dose solution must be discarded and the reason documented by the pharmacist in the study drug accountability records.

Elotuzumab will be administered to each subject as an IV infusion, using an automated infusion pump set at the appropriate rate according to the dose administration section (see Administration Instruction section below). The dose of elotuzumab will be calculated using the subject's predose weight on Day 1 of each cycle (the screening weight can be used for Cycle 1 dose calculation), and then added to 0.9% saline for infusion**.**

Reconstitute elotuzumab lyophilized study drug, as described in steps 1 to 5.

Step 1: For a 440 mg vial of lyophilized elotuzumab, draw 17 mL of Sterile Water for Injection (SWFI), USP into a syringe equipped with an 18-gauge or smaller needle.

Step 2: Remove the flip-top from the elotuzumab vial.

Step 3: Place the vial upright on a flat surface and, using standard aseptic techniques, insert the syringe needle into the vial through the center of the rubber stopper and deliver 17 mL (into the 20-mL vial containing 440 mg elotuzumab) SWFI, USP, into the vial. Slowly remove the syringe needle out of the vial. The final volume of the reconstituted solution is approximately 17.6 mL, which includes the volume displaced by the solid cake. The concentration of elotuzumab in the reconstituted solution is approximately 25 mg/mL.

Step 4: DO NOT SHAKE. Hold the vial upright and gently swirl the solution by rotating the vial

to dissolve the lyophilized cake. Then gently invert the vial a few times in order to dissolve any powder that may be present on top of the vial or the stopper. Finally, hold the vial upright again and gently swirl the solution a few more times to dissolve any remaining particles. Avoid prolonged or vigorous agitation. DO NOT SHAKE.

Step 5: After the remaining solids are completely dissolved, allow the reconstituted solution to stand for 5 to 10 minutes. It is acceptable to have small bubbles and/or foam around the edge of the vial. The reconstituted
preparation results in a colorless to slightly yellow, clear to slightly opalescent solution containing approximately 25 mg/mL of elotuzumab.

Step 6: Once the reconstitution is completed, withdraw the calculated drug volume and further dilute with 100-500 ml of normal saline into an infusion bag (see Pharmacy Manual for additional details). The volume of saline or D5W can be adjusted so as not to exceed 5 mL/kg of patient weight at any given dose of elotuzumab. The resulting elotuzumab concentration must be from 1.0 mg/mL to 6.0 mg/mL. Elotuzumab solutions are compatible with polyvinyl chloride and polyolefin bags. Examples of such bags include Viaflo, MacoPharma Easyflex N, Macoflex N, B Braun Excel, and Braun Ecobag.

Drug volume will be calculated based on subject weight: For example, a subject receiving 10 mg/kg elotuzumab who weighs 80 kg on Day 1 [predose] will require 800 mg of study drug for infusion. Withdraw 32 mL of elotuzumab (25 mg/mL) from 2 vials and add to an infusion bag already containing 230 mL saline, for a total of 262 mL to be infused.
Similarly, an 80 kg subject receiving 20 mg/kg elotuzumab [predose] will require 1600 mg of study drug for infusion. Withdraw 64 mL of elotuzumab (25 mg/mL) from 4 vials and add to an infusion bag already containing 340 mL saline, for a total of 404 mL to be infused.

Use a new sterile needle for withdrawing solution from each vial.

The same vial must not be used to prepare elotuzumab for more than one subject. Used elotuzumab vials will be stored until study drug accountability has been completed by the BMS designee, and destruction or return is authorized. Used vials do not need to be refrigerated.

Note: Subjects must be premedicated as described in Section 5.2 prior to elotuzumab infusion.

Administration Instructions

The first dose of elotuzumab will be administered following premedications (described in Section 5.2) to each subject as an IV infusion, using an automated infusion pump set at an initial rate of 0.5 mL per minute (30 mL/hour). If the subject does not have an infusion reaction within 30 minutes, escalate the infusion rate by 0.5 mL per minute. If the subject still does not have an infusion reaction within 30 minutes, escalate the infusion rate to a maximum of 2 mL per minute (120 mL/hour). If a subject experiences a Grade $\geq$ 2 infusion reaction, the infusion must be interrupted. Please see below for detailed information on the management of infusion reaction and re-initiation of infusion.

The second dose of elotuzumab must be initiated at an infusion rate of 3 mL per minute if no infusion reactions were observed with the first elotuzumab infusion. If the subject does not experience an infusion reaction during the first 30 minutes of the second dose of elotuzumab, escalate the infusion rate to 4 mL per minute.

The third dose of elotuzumab must be initiated at an infusion rate of 5 mL per minute if no infusion reactions were reported with the second elotuzumab infusion.

The fourth and subsequent doses of elotuzumab must be initiated at an infusion rate of 5 mL per minute if no infusion reactions were reported.

On the first dose of escalation to 20mg/kg (Cycle 7 of continuation), patient who have escalated to 5ml/min at 10 mg/kg dose must decrease the rate to 3 mL/min at the first infusion at 20 mg/kg (see Table 2 below).

Elotuzumab Infusion Rate

The elotuzumab infusion rate will be increased gradually to a maximum of 5 mL/min as presented in Table 1. Table 1 represents an example for an 80 kg subject receiving 10mg/kg dose. The total volume varies according to the subject weigh and the elotuzumab administered dose.

Table 1 Elotuzumab Infusion Rate Plan

Infusion Rate	Duration of infusion	Volume delivered	Volume remaining
Cycle 1 Dose 1	Approximate Total Duration: 2hrs 50min		262 mL*
0.5 mL/min	30 min	15 mL	247 mL
1 mL/min	30 min	30 mL	217 mL
2 mL/min	110 min	217 mL	0 mL
Cycle 1 Dose 2	Approximate Total Duration: 1hrs 13min		262 mL
3 mL/min	30 min	90 mL	172 mL
4 mL/min	43 min	172 mL	0 mL
Cycle 1 Dose 3 and 4	Approximate Total Duration: 53min		262 mL
5 mL/min	53 min	262 mL	0 mL
Cycle 2 +	Approximate Total Duration: 53min		262 mL
5 mL/min	53 min	262 mL	0 mL

* Volume for 80 kg subject. Total volume varies according to the subject weight.
Please note that infusion rate increase to the next higher level only if no infusion reactions encountered.

Table 2 Elotuzumab Infusion Rate Plan for 20 mg/kg

Dose 1		**Dose 2 and all subsequent doses**
Time Interval	**Rate**	**Rate**
0-30 min	3 mL/min	5 ml/min
30 min or more	4 mL/min	

Infusion Reactions

If a subject experiences a Grade □□2 infusion reaction, the infusion must be interrupted. Please refer to Appendix D for detailed information on the management of infusion reaction and re-initiation of infusion. If a subject experiences a Grade □□3 elotuzumab infusion reaction that has resolved to Grade □□1, subsequent infusion rate of elotuzumab should be escalated in a stepwise fashion (0.5 mL every 30 minutes as per above).

1. Administer through a low-protein-binding 0.22 - micrometer or smaller in-line filter (placed as proximal to the subject as is practical). Prime the infusion line with study drug before starting the infusion.

2. Set the IV pump to deliver the infusion at the rate of 0.5 mL per minute (including the drug in the line). The total time of infusion will vary depending upon the maximum tolerated mL/min infusion rate as discussed above.

3. Record every time the infusion is started and stopped and the reason why the start and stop occurred.

4. Monitor the IV setup and the subject's IV site frequently during infusion, checking for the correct infusion rate and IV site infiltration.

5. Ensure that the full volume of elotuzumab is infused.

After elotuzumab has been infused from the line, discontinue the infusion, disconnect the IV tubing, and dispose of materials appropriately according to the facility's standard procedure.

Note: Subjects must be premedicated as described in Section 5.2 prior to elotuzumab infusion.

APPENDIX D: Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions

Grade 1 Infusion Reaction

Grade 1 elotuzumab infusion-related reactions by definition do not require intervention; however, increased monitoring is recommended.

Grade 2 or 3 Infusion Reaction

Infusion reactions during the elotuzumab infusion: For a Grade 2 or 3 elotuzumab infusion-related reaction, the infusion must be interrupted. The subject should be treated as clinically indicated with one or more of the following medications or interventions: antiemetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

Once the elotuzumab infusion-related reaction has resolved to Grade $\leq$ 1, the infusion can be restarted at 0.5 mL/minute. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion (0.5 mL/minute every 30 minutes) to the rate at which the infusion reaction occurred. If no recurrence of the infusion reaction, the escalation regimen can be resumed. Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes for 1 or 2 hours after the end of the elotuzumab infusion (as clinically indicated). If the elotuzumab infusion reaction recurs, the infusion must be stopped and not restarted on that day. Appropriate therapy should be administered to address the subject's signs and symptoms. The infusion can be reattempted at the next protocol defined infusion time point at the investigator's discretion with additional premedication as described throughout Section 4.5.4

Infusion reactions after the completion of elotuzumab infusion: Should a Grade 2 or 3 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 infusion on subsequent infusions after a Grade 2 or 3 infusion reaction: Subjects with a Grade 2 or 3 infusion reactions should have the next infusion started at 0.5 mL/min and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes) to the rate at which the infusion reaction occurred.

If no Grade $\geq$ 2 infusion reaction occurs, at the next infusion, the escalation regimen will be resumed starting at the maximum rate achieved during the prior infusion and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes).

Grade 4 Infusion Reaction

Subjects with a Grade 4 elotuzumab infusion reaction must have elotuzumab permanently discontinued.

Elotuzumab Premedication Regimen in Subjects With a Prior Infusion Reaction

To be re-treated with elotuzumab, subjects with a prior infusion reaction must receive H1, H2 blockers and acetaminophen at maximum doses specified (ie, 50 mg diphenhydramine, 50 mg

ranitidine (or equivalent), and 650-1000 mg acetaminophen) 45 to 90 minutes before initiating the elotuzumab.

If a subject with a prior Grade 2 to 3 infusion reaction also requires dose reduction of dexamethasone, the dexamethasone dose on the days of elotuzumab infusion should be no less than 8 mg IV.

Subjects with Grade 4 infusion reaction are not eligible to receive additional elotuzumab. These subjects may continue to receive pomalidomide and dexamethasone.

APPENDIX E: Pomalidomide Pregnancy Prevention Plan for Subjects in Clinical Trials

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving pomalidomide within a clinical trial. The following PPP documents are included:

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 1) provides the following information:
    - Potential risks to the fetus associated with pomalidomide exposure
    - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
    - Requirements for counseling of all subjects receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
    - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving pomalidomide in the study
    - Pregnancy testing requirements for subjects receiving pomalidomide who are FCBP
2. The Pomalidomide Education and Counseling Guidance Document for each gender (female and male; Section 2 and Section 3 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of pomalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Pomalidomide Information Sheet (Section 4) will be given to each subject receiving pomalidomide. The subject must read this document prior to starting pomalidomide and each time the subject receives a new supply of pomalidomide.

1. POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

1.1. Risks Associated with Pregnancy

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it can cause birth defects or death to an unborn baby.

The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

1.1.1. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

1.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

1.2. Counseling

1.2.1. Females of Childbearing Potential

For a FCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting pomalidomide, throughout the entire duration of pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence pomalidomide as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 1.4) and in the Informed Consent
- She acknowledges that she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

1.2.2. Females Not of Childbearing Potential

For a FNCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She acknowledges she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

1.2.3. Males

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time. Therefore, male subjects taking pomalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

1.3. Contraception

1.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting pomalidomide; 2) while taking pomalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of pomalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:

  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

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

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

1.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

1.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while

taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

1.5. Pregnancy Precautions for Pomalidomide Use

1.5.1. Before Starting Pomalidomide

1.5.1.1. Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting pomalidomide.

1.5.1.2. Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

1.5.2. During and After Study Participation

1.5.2.1. Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking pomalidomide, at study discontinuation, and at Day 28 following the last dose of pomalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

1.5.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving pomalidomide, during dose interruptions or for at least 28 days after the last dose of pomalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking pomalidomide, the Investigator must be notified immediately.

1.5.3. Additional Precautions

- Subjects should be instructed to never give pomalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- No more than a 28-day pomalidomide supply may be dispensed with each cycle of pomalidomide.

2. POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

2.1. Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:

   ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. Females of childbearing potential must agree not to become pregnant while taking pomalidomide.

   ☐ That the required pregnancy tests performed are negative.

   ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving pomalidomide, while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide).

   One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

   – Examples of highly effective methods:
     - Intrauterine device (IUD)
     - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
     - Tubal ligation
     - Partner's vasectomy

- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of pomalidomide and at the last dose of pomalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving pomalidomide, one within 10 to 14 days, and a second within 24 hours of the start of pomalidomide.
- Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking pomalidomide if menstrual cycles are regular.
- Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking pomalidomide if menstrual cycles are irregular.
- If the subject missed a period or has unusual menstrual bleeding.
- When the subject is discontinued from the study and at Day 28 after the last dose of pomalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of pomalidomide.

☐ The subject confirmed that she will stop taking pomalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will never share pomalidomide with anyone else.

☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.

☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.

2. I have provided the Pomalidomide Information Sheet to the subject.

2.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:

- ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
- ☐ The subject has not and will never share pomalidomide with anyone else.
- ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
- ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
- ☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.

2. I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving pomalidomide, while receiving pomalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

3. POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking pomalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking pomalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

<u>Do Not Dispense Pomalidomide if:</u>

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4. POMALIDOMIDE INFORMATION SHEET

For subjects enrolled in clinical research studies

Please read this Pomalidomide Information Sheet before you start taking pomalidomide and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rats and rabbits.

   If you are a female who is able to become pregnant:

   - **Do not take pomalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting pomalidomide
     - while taking pomalidomide
     - during breaks (dose interruptions) of pomalidomide
     - for at least 28 days after the last dose of pomalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of pomalidomide
     - 24 hours prior to the first dose of pomalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of pomalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking pomalidomide if you become pregnant while taking pomalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.
   - **Do not breastfeed while taking pomalidomide and for at least 28 days after the last dose of pomalidomide**

- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females whose male partner is receiving pomalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking pomalidomide
  - During breaks (dose interruptions) of pomalidomide
  - For at least 28 days after the last dose of pomalidomide
- **Male subjects should not donate sperm or semen** while taking pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**
   - **Do not share pomalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
   - **Do not donate blood** while you take pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
   - **Do not break, chew, or open pomalidomide capsules at any point.**
   - You will get no more than a 28-day supply of pomalidomide at one time.
   - Return unused pomalidomide capsules to your study doctor.

   Additional information is provided in the informed consent form and you can ask your study doctor for more information.

APPENDIX F: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

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

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

G. Product Complaints

Definition: A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed (refer to Section 8.10).

H. Medication Error

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdose constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact Millennium (see below) and report the event.

I. Pregnancies and Suspected Pregnancies

Pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test in a female subject of reproductive potential, regardless of disease state) occurring while the subject is on study treatment, or within 30 days of the subject's last dose of study treatment, are considered immediately reportable events. Study treatment is to be discontinued immediately.

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Bristol-Myers Squibb and Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event as described in Sections 11.6-11.7.

The female subject should be referred to an obstetrician-gynecologist, (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation and counseling. The Investigator will follow the female subject until completion of the pregnancy outcome and up to 1 year to monitor the baby, and must notify Bristol-Myers Squibb and Celgene Drug Safety immediately about the outcome of the pregnancy.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion, STILLBIRTH, NEONATAL DEATH, OR CONGENITAL ANOMALY) the Investigator should report the abnormal outcome as an SAE. All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to study treatment should also be reported.

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study treatment should notify the Investigator immediately, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with pomalidomide are advised to continue complete abstinence or condom use during treatment and 28 days after stopping treatment.

APPENDIX G: Reporting Timelines

	Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Celgene**	**Bristol Myers-Squibb**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	Report within 24 hours	Report within 24 hours
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	Report within 24 hours	Report within 24 hours
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment			
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.				
A series of minor deviations that are being reported as a	Report within 10 working days.				

continuing noncompliance					
Protocol exception	Approval must be obtained prior to implementing the change				
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB			Report no later than 15 calendar days after it is determined that the information qualifies for reporting		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.				
Breach of confidentiality	Within 10 working days.				
Incarceration	If withdrawing the participant poses a safety issue, report				

	within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.				
Pregnancies				Report within 24 hours	Report within 24 hours

	Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Celgene**	**Bristol Myers-Squibb**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	Report within 24 hours	Report within 24 hours
Minor deviation	Report summary information at the time of continuing review.				
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days.				

	If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.				
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.				

	Expedited Reporting Timelines for Secondary Sites				
Event	**WU (Coordinating Center)**	**Local IRB**	**FDA**	**Celgene**	**Bristol Myers-Squibb**
Serious AND unexpected suspected adverse reaction	Report no later than 11 calendar days after it is determined that the information qualifies for reporting.	Report all applicable events to local IRB according to local institutional guidelines.	The research team at Washington University is responsible for reporting all applicable events to the FDA as needed.	The research team at Washington University is responsible for reporting all applicable events to Millennium as needed.	The research team at Washington University is responsible for reporting all applicable events to Millennium as needed.
Unexpected fatal or life-threatening suspected adverse reaction	Report no later than 4 calendar days after initial receipt of the information.				

	Expedited Reporting Timelines for Secondary Sites				
Event	**WU (Coordinating Center)**	**Local IRB**	**FDA**	**Celgene**	**Bristol Myers-Squibb**
Unanticipated problem involving risk to participants or others	Report no later than 4 calendar days after initial receipt of the information.				
Adverse event or SAE that does not require expedited reporting	As per routine data entry expectations				
Protocol exception	Approval must be obtained prior to implementing the change.				

APPENDIX H: Washington University SAE Reporting Cover Sheet

SAE COVER SHEET- Secondary Site Assessment

Washington University HRPO#:	Sponsor-Investigator:
Subject Initials:	Subject ID:
Treating MD:	Treating Site:
EVENT TERM:	Event Start Date:
EVENT GRADE:	Date of site's first notification:

Treating MD Event Assessment:

Is this event **possibly, probably, or definitely** related study treatment?

☐ yes ☐ no

If yes, please list which drug (if more than one)_____

Explain _____

_____

_____ _____ _____

Physician's Name **Physician's Signature** **Date**