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Title: A Phase II Study of Elotuzumab in Combination with Pomalidomide, Bortezomib, and Dexamethasone in Relapsed and Refractory Multiple Myeloma

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IND #: 129481
IND Sponsor: Andrew Yee, MD
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Bortezomib, commercially available
Dexamethasone, commercially available

Additional reference numbers: Celgene # PO-CL-MM-PI-005363
Bristol-Myers Squibb # CA 204-171
Multiple Myeloma Research Consortium # 075
ClinicalTrials.gov NCT02718833
SCHEMA

Elotuzumab-PVD

Cycles 1-2
Elotuzumab, days 1, 8, 15, 22
Pomalidomide, days 1-21
Bortezomib, days 1, 8, 15
Dexamethasone, days 1, 8, 15, 22

Cycles 3-8
Elotuzumab, days 1, 15
Pomalidomide, days 1-21
Bortezomib, days 1, 8, 15
Dexamethasone, days 1, 8, 15, 22

Cycles 9+ (maintenance)
Elotuzumab, day 1
Pomalidomide, days 1-21
Bortezomib, days 1, 15
Dexamethasone, days 1, 8, 15, 22

Cycle length: 28 days
SYNOPSIS

A Phase II Study of Elotuzumab in Combination with Pomalidomide, Bortezomib, and Dexamethasone in Relapsed and Refractory Multiple Myeloma

Primary objectives

- To evaluate the objective response rate (partial response or better) of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone in patients with relapsed and refractory multiple myeloma and who have received at least one prior therapy and who are refractory to lenalidomide as last line or prior therapy.
- To evaluate the safety profile of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone (elo-PVD).

Secondary objectives

- To evaluate the progression free survival (PFS) of elo-PVD.
- To study clonal evolution, clonal heterogeneity, and correlate with response.
- Correlate response with tumor genotype and expression profile signature.

Study phase

Open label phase II study of the combination of elotuzumab, pomalidomide, bortezomib, and dexamethasone in relapsed and refractory multiple myeloma who have had at least one prior line of therapy. This study will enroll 46 patients.

Key inclusion criteria

1. Relapsed and refractory multiple myeloma with measurable disease according to the International Myeloma Working Group (IMWG) Criteria
2. Patients must have received at least one line of prior therapy with at least two cycles of lenalidomide and at least two cycles of a proteasome inhibitor (either in separate regimens or within the same regimen).
3. Patients must have refractory disease, with disease progression on or within 60 days of completion of last therapy.
4. Patients must be refractory and/or relapsed/refractory to lenalidomide as last or prior therapy.
5. Patient is ≥ 18 years of age
6. ANC ≥ 1,000/µL and platelet count ≥ 50,000/µL. Patients with ANC <1000/µL can be considered for screening on a case by case basis with additional monitoring, after discussion with the P.I.
7. Calculated creatinine clearance of ≥ 30 mL/min according to Cockroft-Gault equation
8. Patient has adequate hepatic function, as evidenced by serum bilirubin values < 2 mg/dL and serum aspartate transaminase (ALT) and/or aspartate transaminase (AST) values < 3 × the upper limit of normal (ULN) of the institutional laboratory reference range.
9. If a female of childbearing potential, patient has a negative urine or serum pregnancy test at baseline (C1D1).
Key exclusion criteria

1. Prior therapy with elotuzumab. Elotuzumab use >5 years prior to screening permitted after discussion with PI.
2. Patient has a history of other malignancies unless has undergone definitive treatment more than 3 years prior to entry into the study and without evidence of recurrent malignant disease. Patients who have completed definitive treatment less than 3 years prior to study entry may be permitted to enroll after discussion with the Principal Investigator. Patients with basal cell carcinoma of the skin; superficial carcinoma of the bladder; carcinoma in situ of the cervix; ductal carcinoma in situ of the breast; or incidental histologic finding of prostate cancer managed with surveillance are eligible to participate.
3. Patient has known human immunodeficiency virus (HIV positive) or hepatitis B surface antigen-positive status or is known to have an active hepatitis C infection.
4. Patient has a history of significant cardiovascular, neurological, endocrine, gastrointestinal, respiratory, or inflammatory illness that could preclude study participation, pose an undue medical hazard, or interfere with the interpretation of the study results, including, but not limited to, patients with congestive heart failure (New York Heart Association [NYHA] Class 3 or 4); unstable angina; cardiac arrhythmia; recent (within the preceding 6 months) myocardial infarction or stroke; hypertension requiring > 2 medications for adequate control; diabetes mellitus with > 2 episodes of ketoacidosis in the preceding 12 months; or chronic obstructive pulmonary disease (COPD) requiring > 2 hospitalizations in the preceding 12 months.
5. Patient has any other medical, psychiatric, or social condition that would preclude participation in the study, pose an undue medical hazard, interfere with the conduct of the study, or interfere with interpretation of the study results.
6. Patient has known hypersensitivity to immunomodulatory drugs (IMiDs, e.g. thalidomide, lenalidomide, pomalidomide).
7. Patient is currently enrolled in another clinical research study involving an investigational agent and/or is receiving an investigational agent for any reason.

Treatment plan

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Elotuzumab</th>
<th>Pomalidomide</th>
<th>Bortezomib</th>
<th>Dexamethasone†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>10 mg/kg i.v. on days 1, 8, 15, 22</td>
<td>4 mg p.o. qd on days 1-21</td>
<td>1.3 mg/m² s.c. on days 1, 8, 15</td>
<td>On weeks without elo: dex 40 mg p.o. on days 1, 8, 15, 22; on weeks with elo: dex 28 mg p.o. (3-24 hrs prior to elo) and dex 8 mg iv</td>
</tr>
<tr>
<td>3-8</td>
<td>10 mg/kg i.v. on days 1, 15</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>9+</td>
<td>20 mg/kg i.v. on day 1</td>
<td>Same as above</td>
<td>1.3 mg/m² s.c. on days 1, 15</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

Treatment cycle is 28 days.
†Refer to protocol for details of premedication prior to elotuzumab. Oral dexamethasone dose may be split over two days.
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1. OBJECTIVES

1.1 STUDY DESIGN

This is an open label phase II study that will enroll 46 patients with relapsed and refractory multiple myeloma who have received at least one prior therapy and who have had previous treatment with both lenalidomide and bortezomib and who are refractory to lenalidomide as last line or prior therapy.

1.2 PRIMARY OBJECTIVES

- To evaluate the objective response rate (partial response or better) of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone in patients with relapsed and refractory multiple myeloma and who have received at least one prior line of therapy and have had received prior lenalidomide and bortezomib and who are refractory to lenalidomide as last line or prior therapy.
- To evaluate the safety profile of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone (elotuzumab-PVD).

1.3 SECONDARY OBJECTIVES

- To evaluate the progression free survival (PFS) of elotuzumab-PVD.
- To study clonal evolution, clonal heterogeneity, and correlate with response.
- Correlate response with tumor genotype and expression profile signature.

2. BACKGROUND

2.1 STUDY DISEASE

Multiple myeloma (MM) is an incurable plasma cell malignancy and the second most common hematologic malignancy in the United States. There has been a dramatic increase in response rates in MM achieved over the past several years with newer agents such as lenalidomide and bortezomib and in combination as RVD as front line therapy in newly diagnosed disease (Richardson et al., 2010). However, the majority of subjects with myeloma will relapse or become refractory, regardless of the line of therapy. The rate of complete response in relapsed disease, and particularly in refractory, relapsed disease, remains relatively low with substantial opportunity for improvement. Patients who are refractory to newer agents such as bortezomib have a poor prognosis, with a median event free survival of five months and median overall survival of nine months (Kumar et al., 2012). There is a significant, unmet need for novel strategies to treat these patients with refractory disease.
2.2 STUDY AGENTS

2.2.1 Elotuzumab

Elotuzumab (BMS-901608; formerly known as HuLuc63) is a humanized recombinant monoclonal IgG1 antibody product directed to human CS1 (CD2-subset-1, also known as CRACC and SLAMF7), a cell surface glycoprotein that is highly expressed in MM cells. The proposed mechanism of action of elotuzumab involves natural killer (NK) antibody dependent cell-mediated cytotoxicity (ADCC), since elotuzumab can also kill MM cell lines in vitro in the presence of peripheral blood mononuclear cells (PBMCs) or purified NK cells. Because of its potent antitumor activity, elotuzumab is being developed as a clinical candidate for the treatment of MM.

The first three trials (HuLuc63-1701, HuLuc63-1702, and HuLuc63-1703) were phase 1 studies in relapsed MM subjects with elotuzumab as monotherapy or combined with bortezomib or lenalidomide, respectively. Results of the monotherapy Phase 1 trial (HuLuc63-1701) demonstrated acceptable safety with no maximum tolerated dose (MTD) identified up to 20 mg/kg. Stable disease was reported for 27% of the 35 subjects treated. Data from HuLuc63 1702 (combination with bortezomib/dexamethasone) demonstrated adequate safety with no MTD observed up to 20 mg/kg and an ORR of 48% among 28 subjects. Preliminary data from the Phase 1 portion of HuLuc63-1703 (CA204-003, combination with lenalidomide and dexamethasone) demonstrated acceptable safety with no MTD observed up to 20 mg/kg and an ORR of 82% among the 28 evaluable subjects. The HuLuc63-1703 (CA204-003) trial also included a phase 2 portion that is ongoing. Preliminary data from this portion of the trial demonstrated an ORR of 84% among all 73 treated subjects, 92% among the 36 subjects treated with 10 mg/kg of elotuzumab. Median PFS was 33 months with the 10 mg/kg dose and 18.6 months with the 20 mg/kg dose.

Recently, a phase III study, ELOQUENT-2, compared the combination of elotuzumab, lenalidomide, and dexamethasone to lenalidomide and dexamethasone in patients with relapsed disease who have had one to three prior lines of therapy (Lonial et al., 2015). This study found that the elotuzumab-containing arm had superior progression free survival, 19.4 months v. 14.9 months in the control group. The overall response rate was also higher, 79% v 66%. Side effects were similar between both arms, except for infusion reactions with elotuzumab. Based on the results of this study, elotuzumab was approved by the FDA in November 2015 for the treatment of relapsed MM.

2.2.1.1 Infusion reactions

Most biologics carry a risk for infusion reactions. Infusion reactions typically develop during the infusion or shortly thereafter, vary in symptom severity from mild to potentially life threatening and are commonly associated with a variety of signs and symptoms.

The mechanisms by which monoclonal antibodies elicit infusion reactions remain unclear.
- Monoclonal antibodies may interact with their molecular targets on circulating blood cells, tumor cells, or effector cells recruited to the tumor site (e.g., rituximab with CD20), thereby promoting the release of inflammatory cytokines.
- Infusion reactions may have a hypersensitivity component, in which the molecular structure of the drug or a component of the drug formulation is recognized as an antigen by the immune system. IgE mediated events are rare but possible.
- Non-immune-mediated “hypersensitivities” are frequent following monoclonal or polyclonal antibody administration. This reaction resembles immune mediated reactions but an immune mechanism is not detectable. The majority of these reactions imitate the clinical features of milder immediate reactions (erythema, urticaria), but greater severity, even a lethal outcome are possible.

There is no difference between the clinical manifestations of immune-mediated and non-immune-mediated reactions. They both may involve the cutaneous, respiratory, gastrointestinal, or cardiovascular systems. The management of both types of reactions is the same; in addition, in the literature the two terms are often used interchangeably to describe infusion-related reactions.

The key elotuzumab related events have been infusion related AEs in all studies. Infusion reactions have been mitigated with premedications consisting of corticosteroids, H1 and H2 antagonists, and acetaminophen. Prior to the initiation of an adequate premedication regimen in the phase 1 trial, infusion reactions were observed in 52-89% of subjects.

The most frequent elotuzumab peri-infusional AEs that occurred in ≥ 10% of subjects across all Phase 1 studies, regardless of causality, include nausea, vomiting, chills, infusion-related reaction, flushing, dyspnea, cough, headache, dizziness, and rash.

Two subjects in the HuLuc63-1701 and HuLuc63-1702 trial experienced G3 infusion reactions (Grade 3 hypersensitivity).

Based on preliminary data from the single-arm elotuzumab studies HuLuc63-1703 (CA204003, lenalidomide combination), CA204005 (lenalidomide combination), CA204007 (lenalidomide combination), CA204010 (thalidomide combination), and CA204011 (elotuzumab monotherapy), following the administration of a premedication regimen, infusion reactions were noted in approximately 11% of subjects. Four subjects experienced a Grade 3/4 infusion reaction. The most common symptoms of an elotuzumab infusion reaction were pyrexia and nausea. The most severe (Grade 3) infusion reaction was rash.

### 2.2.2 Pomalidomide

Pomalidomide is an approved third generation immunomodulatory drug that in combination with dexamethasone, was found to be effective for patients who have progressed after prior bortezomib and lenalidomide treatment (San Miguel et al., 2013). A phase I trial of pomalidomide with bortezomib and dexamethasone (PVD) (MM-005) was well tolerated and
showed an ORR of 71% (Richardson et al., 2013). This combination is being investigated in a phase III trial (MM-007).

2.2.3 Bortezomib

Bortezomib is a proteasome inhibitor approved for the treatment of relapsed or refractory myeloma based on the results of a phase III trial (APEX trial) comparing bortezomib to high dose dexamethasone (Richardson et al., 2005).

In newly-diagnosed patients, combination of bortezomib plus MP was superior to MP alone with respect to response, remission duration, and overall survival (San Miguel et al., 2008). More recently, subcutaneous bortezomib was compared to intravenous bortezomib in a randomized, phase III non-inferiority study involving patients with relapsed disease and found to be equivalent in terms of efficacy and importantly, significantly less peripheral neuropathy (Moreau et al., 2010).

Preclinical evidence of synergy between lenalidomide and bortezomib provided rationale for combination therapy with lenalidomide and bortezomib. A phase II multicenter study in newly-diagnosed patients found that the combination of lenalidomide, bortezomib, and dexamethasone (RVD) showed that the overall response rate was 100% (Richardson et al., 2010).

2.2.4 Dexamethasone

Glucocorticoids such as dexamethasone have significant activity in myeloma. They are a core component of treatment regimens in newly-diagnosed patients and in relapsed and refractory disease. For example, in a study of 112 patients with untreated myeloma, the response rate with dexamethasone alone was 43% (Alexanian et al., 1992). Combination of dexamethasone with novel agents like bortezomib or lenalidomide from several phase II trials suggests that the addition of dexamethasone consistently increases response rates from 25-30% to 50-60% (Jagannath et al., 2004; Richardson et al., 2006; Weber et al., 2003).

In this treatment, there is a combination of oral and intravenous dexamethasone for both treatment and to minimize risk of infusion reactions. Since oral dexamethasone has 76% bioavailability compared to intravenous dexamethasone (Czock et al., 2005), the combination of PO and IV dexamethasone used in this study maintain equivalent weekly dexamethasone exposure.

2.3 RATIONALE

The combination of elotuzumab with lenalidomide and dexamethasone showed high response rates in patients with relapsed or refractory MM (Lonial et al., 2012) in phase 1-2 clinical trials, and this finding was confirmed in the phase III study, ELOQUENT-2 (Lonial et al., 2015).

Bortezomib may enhance the activity of elotuzumab. Bortezomib treatment of myeloma cells
was shown to down modulate cell-surface expression of MHC class I, an inhibitor of NK cell function, was seen following bortezomib treatment of myeloma cells (Shi et al., 2008). This finding lends further support to the hypothesis that treatment of myeloma cells with bortezomib may render them more susceptible to elotuzumab-mediated ADCC.

In vitro testing of the bortezomib and elotuzumab combination using ADCC assays showed enhanced elotuzumab-mediated ADCC against OPM2 myeloma cells using NK effector cells from healthy donors (van Rhee et al., 2009). Additionally, patient-derived NK cells induced approximately 20% specific lysis of autologous myeloma cells in the presence of elotuzumab (10 μg/mL) alone with a dose-dependent increase in specific lysis with the addition of bortezomib. Finally, experiments with OPM2 tumor-bearing mice demonstrated profound reduction in the rate of tumor growth from the addition of bortezomib to elotuzumab and activity that was significantly superior to bortezomib or elotuzumab alone. A trial comparing the combination of elotuzumab with bortezomib and dexamethasone v. bortezomib dexamethasone in MM patients with 1-3 prior lines of therapy was recently presented. (Palumbo et al., 2015). The elotuzumab containing arm had significant improvement in progression free survival, 9.7 v. 6.9 months. Adverse events were similar in both arms, except for infrequent grade 1-2 infusion related reactions.

Given these findings, the combination of elotuzumab with pomalidomide, bortezomib, and low dose dexamethasone may offer a compelling and unique therapeutic advance for this challenging patient population

2.4 **CORRELATIVE STUDIES BACKGROUND**

The following exploratory studies may be performed:

1. Elaborate the subclonal heterogeneity of disease present in individual MM patients with relapsed and refractory high risk disease using whole exome and transcriptome sequencing of MM circulating tumor cells.

2. Determine the evolution of mutations and subclonal heterogeneity in MM patients longitudinally while undergoing treatment in a phase II trial of elotuzumab, pomalidomide, bortezomib, and dexamethasone.

3. Explore the relationship between subclonal heterogeneity and known markers of high risk disease such as high risk FISH and cytogenetics.

4. Explore the relationship between myeloma expression profiles and disease response.
3. PARTICIPANT SELECTION

3.1 ELIGIBILITY CRITERIA

3.1.1 All laboratory assessments should be performed within 21 days of initiation of protocol therapy unless otherwise specified.

3.1.2 Participant has given voluntary signed written informed consent before performance of any study-related procedure that is not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to their future medical care.

3.1.3 Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (see Appendix A).

3.1.4 Age ≥ 18 years

3.1.5 Measurable disease of multiple myeloma as defined by at least one of the following:
- Serum monoclonal protein ≥ 0.5 g/dL
- ≥ 200 mg of monoclonal protein in the urine on 24 hour electrophoresis
- Serum free light chain ≥ 100 mg/L (10 mg/dL) and abnormal serum free kappa to serum free kappa light chain ratio

3.1.6 Previously treated relapsed and refractory multiple myeloma
- Patients must have received at least one prior line of therapy
- Prior therapy must include at least 2 cycles of lenalidomide and at least 2 cycles of a proteasome inhibitor (either in separate regimens or within the same regimen)
- Patients must be refractory and/or relapsed/refractory to lenalidomide or prior lenalidomide.
- Disease progression on or within 60 days of completion of last therapy.

3.1.7 ANC ≥ 1000/µL. G-CSF is not permitted within 14 days of screening. Patients with ANC < 1000/µL can be considered for screening on a case by case basis with additional monitoring, after discussion with the PI.

3.1.8 Platelet count ≥ 50,000/µL. Platelet transfusion is not permitted within 7 days of screening.

3.1.9 Hemoglobin ≥ 8 g/dL. Red blood cell transfusions are permitted to meet eligibility criteria.

3.1.10 Calculated creatinine clearance of ≥ 30 mL/min according to Cockroft-Gault equation

3.1.11 Patient has adequate hepatic function, as evidenced by serum bilirubin values < 2 mg/dL and serum aspartate transaminase (ALT) and/or aspartate transaminase (AST) values < 3 × the upper limit of normal (ULN) of the institutional laboratory reference range. Patients with elevated bilirubin due to Gilbert’s syndrome may be permitted with PI approval.

3.1.12 Must be able to take acetylsalicylic acid (ASA) daily as prophylactic anticoagulation.
Patients intolerant to ASA may use low molecular weight heparin or equivalent. Warfarin will be allowed provided patient is full anticoagulated, with an INR of 2-3.

3.1.13 All study participants must be registered into the mandatory POMALYST REMS program, and be willing and able to comply with the requirements of the POMALYST REMS program.

3.1.14 Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Pomalist REMS program.

3.1.15 Able to swallow capsules whole (pomalidomide capsules cannot be crushed, dissolved or broken).

3.2 **EXCLUSION CRITERIA**

3.2.1 Prior therapy with elotuzumab

3.2.2 Participants who have had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier. Patients may have received dexamethasone within 2 weeks prior to entering study.

3.2.3 Participants who are receiving any other investigational agents.

3.2.4 Concomitant high dose corticosteroids except patients may be on chronic steroids (maximum dose 10 mg/day prednisone equivalent) if they are being given for disorders other than myeloma, e.g. adrenal insufficiency, rheumatoid arthritis, etc.

3.2.5 Pregnant or lactating females

3.2.6 Prior history of malignancies, other than MM, unless the patient has completed definitive treatment and has been free of the disease for ≥ 3 years. Patients who are free of disease <3 years may enroll after discussion with the Principal Investigator. Exceptions include the following (i.e. the following are eligible to participate):

- Basal or squamous cell carcinoma of the skin
- Carcinoma in situ of the cervix
- Ductal carcinoma in situ of the breast
- Incidental histologic finding of prostate cancer (T1a or T1b) managed with surveillance

3.2.7 Another malignancy undergoing active treatment with the exception of non-melanoma skin cancer or in situ cervical cancer.

3.2.8 Patients with plasma cell leukemia, POEMS syndrome, or amyloidosis are excluded from this trial.

3.2.9 Known HIV infection

3.2.10 Known active hepatitis B or active hepatitis C infection. Participants who have prior hepatitis C infection but who have received an antiviral treatment and show no detectable viral RNA for 6 months after completion of treatment are eligible.

3.2.11 Peripheral neuropathy ≥ grade 2 despite supportive therapy.
3.2.12 Hypersensitivity to thalidomide, lenalidomide, pomalidomide, bortezomib, or dexamethasone (such as Stevens-Johnson syndrome). Rash to immunomodulatory drug that can be medically managed is allowable.

3.2.13 Allogeneic stem cell transplant less than 12 months prior to initiation of study treatment and who have not discontinued immunosuppressive treatment for at least four weeks prior to initiation of study treatment and who are currently dependent on such treatment. Patients may also not have active graft v. host disease.

3.2.14 Patient has a history of significant cardiovascular, neurological, endocrine, gastrointestinal, respiratory, or inflammatory illness that could preclude study participation, pose an undue medical hazard, or interfere with the interpretation of the study results, including, but not limited to, patients with congestive heart failure (New York Heart Association [NYHA] Class 3 or 4); unstable angina; cardiac arrhythmia; recent (within the preceding 6 months) myocardial infarction or stroke; hypertension requiring > 2 medications for adequate control; diabetes mellitus with > 2 episodes of ketoacidosis in the preceding 12 months; or chronic obstructive pulmonary disease (COPD) requiring > 2 hospitalizations in the preceding 12 months.

3.2.15 Patient has any other medical, psychiatric, or social condition that would preclude participation in the study, pose an undue medical hazard, interfere with the conduct of the study, or interfere with interpretation of the study results.

3.3 INCLUSION OF WOMEN AND MINORITIES

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

4. REGISTRATION PROCEDURES

4.1 GENERAL GUIDELINES FOR DF/HCC AND DF/PCC INSTITUTIONS

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant’s registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.
4.2 **Registration Process for DF/HCC and DF/PCC Institutions**

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 **General Guidelines for Other Investigative Sites**

Eligible participants will be entered on study centrally at Massachusetts General Hospital by the Coordinating Center. All sites should contact the Coordinating Center to verify treatment availability.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator/Sponsor. If a participant does not receive protocol therapy following registration, the participant’s registration on the study must be canceled. The Coordinating Center should be notified of cancellations as soon as possible.

4.4 **Registration Process for Other Investigative Sites**

To register a subject, the following documents should be completed by the participating institution and forwarded to the Coordinating Center at ccpo-mcgroup@partners.org:

- Copy of source documentation for inclusion/exclusion criteria and screening procedures, including but not limited to
  - Pathology report
  - Medical history and physical exam
  - Laboratory reports
  - Concomitant medication list
- Demographics information.
- Signed study consent form.
- Study Entry Note
- HIPAA authorization form, if applicable
- Eligibility checklist

The Coordinating Center will review the above documentation to confirm eligibility and consent. To complete the registration process, the Coordinating Center will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. Once registered a confirmation email with the participant study number, and if applicable the dose treatment level, will be sent to the participating site.

**NOTE:** Registrations can only be conducted by the Coordinating Center during the business hours of 8:30 AM and 5:00 PM Eastern Standard Time (or Eastern Daylight Time when applicable), Monday through Friday. A complete registration packet, including all documents...
listed above, must be received at least 24 hours prior to the anticipated registration to ensure adequate review. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

5. TREATMENT PLAN

5.1 TREATMENT REGIMEN

Treatment will be administered on an outpatient basis.

A treatment cycle is 28 days long.

Expected toxicities and potential risks as well as dose modifications for elotuzumab, pomalidomide, bortezomib, and dexamethasone are described in Section 7.1 Expected Toxicities.

Subjects will remain on study until disease progression, unacceptable toxicity, or withdrawal of patient consent. With the exception of subjects who had disease progression at study discontinuation, all subjects will continue to be evaluated until disease progression, initiation of new therapy, death, or study completion. The study will be completed 60 days after the last participant remaining on study discontinues treatment.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat multiple myeloma.

The first five patients who complete cycle 1 will be assessed for safety and adverse events prior to enrolling all other patients.

5.1.1 Cycles 1-2

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elotuzumab</td>
<td>10 mg/kg</td>
<td>IV</td>
<td>Days 1, 8, 15, 22</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>4 mg</td>
<td>PO</td>
<td>Days 1-21</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m²</td>
<td>SC</td>
<td>Days 1, 8, 15</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>See section on premedication</td>
<td></td>
<td>Days 1, 8, 15, 22</td>
</tr>
</tbody>
</table>

A treatment window of ± 3 days is allowed for cycles 1-2. Doses that fall outside this window are skipped.
5.1.2 Cycles 3-8

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elotuzumab</td>
<td>10 mg/kg</td>
<td>IV</td>
<td>Days 1, 15</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>4 mg</td>
<td>PO</td>
<td>Days 1-21</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m²</td>
<td>SC</td>
<td>Days 1, 8, 15</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>See section on premedication</td>
<td></td>
<td>Days 1, 8, 15, 22</td>
</tr>
</tbody>
</table>

A treatment window of ±7 days is allowed for cycles 3-8. Doses that fall outside this window are skipped.

5.1.3 Cycles 9+

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elotuzumab</td>
<td>20 mg/kg*</td>
<td>IV</td>
<td>Days 1</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>4 mg</td>
<td>PO</td>
<td>Days 1-21</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m²</td>
<td>SC</td>
<td>Days 1, 15</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>See section on premedication</td>
<td></td>
<td>Days 1, 8, 15, 22</td>
</tr>
</tbody>
</table>

*Note dose increase in elotuzumab to 20 mg/kg with maintenance treatment, with cycles 9+.

A treatment window of ± 7 days is allowed for cycles 9+. Doses that fall outside this window are skipped.

5.1.4 Premedication Before Elotuzumab in Patients Without a Reaction

In this treatment, there is a combination of oral and intravenous dexamethasone for both treatment and to minimize risk of infusion reactions. Since oral dexamethasone has 76% bioavailability compared to intravenous dexamethasone (Czock et al., 2005), the combination of PO and IV dexamethasone used in this study maintain equivalent weekly dexamethasone exposure.

On weeks without elotuzumab, administer the weekly dose of 40 mg dexamethasone orally per schedule described above.

The oral dexamethasone dose may be given as a split dose over 2 consecutive days, at the investigator’s discretion.

On weeks of elotuzumab infusion, split the weekly dose of dexamethasone between oral and IV administration as follows:

1. Dexamethasone 28 mg PO between 3-24 hours prior to the start of elotuzumab infusion
   OR as a split dose 12-24 hours (i.e. 12 mg) and 3 hours prior to elotuzumab (i.e. 16 mg)
   AND
2. Dexamethasone 8 mg IV on the day of elotuzumab infusion 45-90 mins prior to the start of infusion.

3. H1 blocker: diphenhydramine (25-50 mg PO or IV) or equivalent 45-90 mins prior to the start of infusion

4. H2 blocker: ranitidine (50 mg IV) or equivalent, 45-90 mins prior to the start of infusion

5. Acetaminophen (650-1000 mg PO), 45-90 mins prior to the start of infusion

5.1.5 Premedication Before Elotuzumab in Patients with a Prior Infusion Reaction

Subjects with prior infusion reaction must receive H1, H2 blockers and acetaminophen at maximum doses specified above.

In addition, dexamethasone premedication should be administered as per table below.

**Corticosteroid premedication**

<table>
<thead>
<tr>
<th>Prior infusion reaction</th>
<th>Corticosteroid premedication prior to elotuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or only grade 1 infusion reaction</td>
<td>28 mg PO dexamethasone (3-24 hrs prior to elotuzumab) AND 8 mg IV dexamethasone at least 45-90 min prior to elotuzumab</td>
</tr>
<tr>
<td>Prior grade 2 infusion reaction</td>
<td>28 mg PO dexamethasone (3-24 hrs prior to elotuzumab) AND 10 mg IV dexamethasone at least 45-90 min prior to elotuzumab</td>
</tr>
<tr>
<td>Prior Grade 3 or recurrent Grade 2 infusion reaction</td>
<td>8 mg oral dexamethasone (12-24 hrs prior to elotuzumab) AND 8 mg oral dexamethasone (at least 3 hrs prior to elotuzumab) AND 18 mg IV dexamethasone at least 45-90 min prior to elotuzumab</td>
</tr>
</tbody>
</table>

At the discretion of the investigator, the 28 mg oral dexamethasone component may be given as a split dose: 12 mg PO (12-24 hours prior to elotuzumab) AND 16 mg PO (3 hours prior to elotuzumab).

If a subject with a prior infusion reaction also requires dose reduction of dexamethasone, the weekly dexamethasone on the days of elotuzumab infusion should be no lower than 8 mg IV (on the day of elotuzumab infusion at least 45 minutes prior to elotuzumab).

Subjects with a Grade 4 elotuzumab infusion reaction must have elotuzumab permanently discontinued. These subjects may continue to stay on the trial and receive pomalidomide, bortezomib, and dexamethasone.

5.2 **PRE-TREATMENT CRITERIA**

5.2.1 **Day 1 of all cycles**

- ANC ≥ 1,000/μL. G-CSF is permitted except for screening and for C1D1. Patients with ANC <1000/μL can be considered for screening on a case by case basis with additional monitoring, after discussion with the PI. Additional monitoring may include more frequent CBCD, mid week, as per local practice, in management of patients undergoing
treatment. G-CSF may be used as per local practice for management of neutropenia.

- Platelet count ≥ 50,000/μL. Platelet transfusions are permitted except for screening.
- Any pomalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1.
- Any pomalidomide or bortezomib-related adverse event that may have occurred has resolved to ≤ grade 2.
- Grade 1 with pain or grade 2 peripheral neuropathy requires dose modification of bortezomib, and grade 2 peripheral neuropathy with pain requires that bortezomib be held.
- Herpes zoster lesions, if present, are dry.
- The maximum amount of time for which a drug may be held due to toxicity is 3 weeks. If drug is held for more than 3 weeks due to toxicity, the participant will be removed from study treatment. However, treatment delay for reasons other than toxicity for more than 3 weeks (for any study treatment) will require authorization from the PI/Sponsor. Dose modification guidelines are described in Section 6. Dosing Delays/Dose Modifications.
- If there were dose modifications or delays in the previous cycle, use the following guidelines:
  - If pomalidomide was held during the previous cycle and restarted at a reduced dose level, without interruption for the remainder of the cycle, then the reduced dose level will be initiated on Day 1 of the new cycle.
  - If pomalidomide dosing was omitted for the remainder of the previous cycle or if a new cycle is delayed due to pomalidomide-related toxicity encountered on the scheduled Day 1, then the new cycle will be started with one-level dose reduction.
  - If any two or more doses of bortezomib were held during the cycle (either consecutively or two or more in one cycle), then the new cycle will be started with one level dose reduction.
  - If the new cycle is delayed due to bortezomib-related toxicity encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction.

5.2.2 Intra-cycle dosing

For intra-cycle dosing with bortezomib on Days 8, 15, the following criteria must be met:
- ANC ≥ 750/μL (G-CSF is permitted)
- Platelet count ≥ 30,000/μL (platelet transfusion support is permitted)

Intra-cycle dose modifications for all drugs will be allowed based on toxicity and according to dose modifications outlined in Section 6.
5.3 **AGENT ADMINISTRATION**

5.3.1 **Elotuzumab**

Administer elotuzumab 30 to 90 minutes following bortezomib when both drugs are given on the same day. Elotuzumab will be administered to each subject as an IV infusion, using an automated infusion pump set at the appropriate rate according to the instructions provided in Appendix F: Preparation and Administration of Elotuzumab.

Vital signs (body temperature, respiratory rate, seated blood pressure, and heart rate) will be recorded as follows. Blood pressure, respiratory rate and heart rate should be measured after the participant has been seated quietly for at least 5 minutes prior to dosing of elotuzumab. Participant will have vital signs measured as follows:

- Prior to pre-medication administration for elotuzumab
- Prior to the start of the elotuzumab infusion
- Thirty minutes after the start of infusion
- At the end of the infusion
- Thirty and 120 minutes post completion of the elotuzumab infusion for Induction Cycles 1 and 2
- Cycle 3 and beyond post infusion vital signs will be measured at 30 minutes
- Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes during and for 2 hours after the end of the elotuzumab infusion

5.3.1.1 **Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions**

**Grade 1 Infusion Reaction During Elotuzumab Infusion**

For Grade 1 elotuzumab infusion-related reactions, consider temporary interruption of infusion or slowing of infusion rate and treatment with supportive measures, as clinically indicated. Unless symptoms worsen, the infusion can resume or continue as planned.

**Grade 2-3 Infusion Reaction During Elotuzumab Infusion**

Infusion reactions during the elotuzumab infusion: For a Grade $\geq 2$ 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: anti-emetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures.

For Grade 2 infusion reactions, once the elotuzumab infusion-related reaction has resolved to Grade 1, the infusion can be restarted at the same rate of infusion at which the infusion reaction occurred. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion according to the Appendix. For Grade 3 infusion reactions, once the elotuzumab infusion-related reaction has resolved to Grade 1, the infusion can be restarted at...
one level lower than the rate of infusion at which the infusion reaction occurred. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion. However, final determination about the rate of infusion will be determined by the treating physician and may be considered on a case-by-case basis. Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes during and for 2 hours after the end of the elotuzumab infusion. 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 in Section 5.3.

### Infusion Reactions After the Completion of Elotuzumab Infusion

Should a Grade $\geq 2$ infusion reaction occur following completion of an elotuzumab infusion, the subject should be treated as clinically indicated with one 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.

Subsequent elotuzumab infusion after a prior Grade 2 or 3 infusion reaction: Subjects with prior Grade 2 infusion reactions should have the subsequent infusion started at the same rate of infusion at which the infusion reaction occurred and the infusion rate may be escalated in a stepwise fashion to a maximum of 5 mL per minute. Subjects with prior Grade 3 infusion reactions should have the subsequent infusion started at one level lower than the rate of infusion at which the infusion reaction occurred. See Appendix F for guidelines regarding escalation of the infusion rate.

### Grade 4 Infusion Reaction

Elotuzumab must be permanently discontinued. Subjects may continue with pomalidomide, bortezomib, and dexamethasone per protocol.

#### 5.3.2 Pomalidomide

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. 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.

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. Pomalidomide will be sent to the research pharmacy.
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 is to be administered at least 2 hours after completion of elotuzumab.

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.

Vomited doses of pomalidomide are not made up.

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.

A drug diary will be provided to participants to record oral administration of doses.

5.3.3 Bortezomib

Bortezomib will be given subcutaneously according to institutional practice.

5.3.4 Dexamethasone

Dexamethasone will be given according to institutional practice.

Each oral dexamethasone dose should be taken with food and at the same time each day. During the days when elotuzumab is not given, if a dose is missed or vomited, the dose should not be made up and the participant should continue with regular scheduling of the drug. On the days of elotuzumab, the investigator should be notified if the oral dose is missed to determine if it should be made up prior to the elotuzumab infusion.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Required Concomitant Therapy

- Prophylaxis against herpes zoster with acyclovir (400 mg po bid) or equivalent antiviral therapy per institutional guidelines and at the discretion of the site investigator, unless the participant develops a hypersensitivity to the agents. The dose may be adjusted for patients with renal insufficiency.
- Prophylaxis against thrombotic events associated with pomalidomide. Participants should receive aspirin (81 or 325 mg) daily. Note, patients at high-risk for thromboembolic disease, such as those with prior history of DVT, should receive anticoagulation with low molecular weight heparin or warfarin or equivalent. It is recommended that if the platelet count falls below 50,000/μL, prophylaxis be held to minimize the risk of bleeding and then resumed when platelet counts are equal to or
5.5 **CRITERIA FOR TAKING A PARTICIPANT OFF PROTOCOL THERAPY**

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

The reason for taking a participant off treatment, and the date the participant was removed, must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the DF/HCC research team updates the relevant Off Treatment/Off Study information in OnCore for participants at their site. The Coordinating Center updates the relevant Off Treatment/Off Study information in OnCore for external Participating Sites.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the overall PI, Andrew Yee, MD, at 617-726-2000 and the Coordinating Center at ccpo-mcgroup@partners.org.

5.6 **DURATION OF FOLLOW UP**

Participants will be followed every three months after removal from protocol therapy or until confirmation of progressive disease, initiation of subsequent myeloma therapy, death, withdrawal of consent, or loss of follow up, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. The first follow up visit should occur three months after the end of treatment visit.

Following disease progression or initiation of subsequent myeloma therapy, participants may be followed-up for survival by telephone contact or chart review every 3 months, for a period
of five years from study enrollment.

5.7 **CRITERIA FOR TAKING A PARTICIPANT OFF STUDY**

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). The DF/HCC research team updates the relevant Off Study information in OnCore for participants at their site. The Coordinating Center updates the relevant Off Study information in OnCore for external Participating Sites.

6. **DOsing DELAYS/DOSE MODIFICATIONS**

Dose reduction of the individual drug(s) most likely causing toxicity is permitted at the investigator’s discretion.

6.1 **ELOTOZUMAB**

No dose reductions are permitted for elotuzumab.

6.2 **POMALIDOMIDE**

See Section 5.2. Pre-Treatment Criteria.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If pomalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. If pomalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction of pomalidomide.

Dose re-escalation of pomalidomide is permitted at the treating physician’s discretion.

**Instructions for Pomalidomide Dose Modifications or Interruption During a Cycle.**
Toxicity | Dose Modification
--- | ---
Neutropenia | Hold the dose for remainder of cycle. If the participant was not receiving G-CSF therapy, G-CSF therapy may be started at the discretion of the treating physician. On Day 1 of the next cycle, the dose of pomalidomide may be maintained if neutropenia was the only significant AE and G-CSF treatments are continued. Otherwise, decrease by one dose level at start of next cycle.

Thrombocytopenia | Hold the dose for remainder of cycle. Decrease by one dose level when dosing is resumed at next cycle

Rash = grade 3 | Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to ≤ grade 1).

Rash = grade 4 or blistering | Discontinue subject from pomalidomide treatment regimen.

Constipation ≥ grade 3 | Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (constipation must resolve to ≤ grade 2).

VTE ≥ grade 3 | Hold dose for remainder of cycle. Initiate anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.

Hypo/hyperthyroidism ≥ grade 2 | Hold dose for remainder of cycle. Initiate appropriate medical therapy. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.

Peripheral neuropathy = grade 3 | Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (neuropathy must resolve to ≤ grade 1).

Peripheral neuropathy = grade 4 | Discontinue subject from pomalidomide treatment regimen.

Infection or viral illness | Day 1 of cycle. Delay cycle until infection/viral illness has resolved. Resume treatment at the same dose level. Do not dose reduce. Intra-cycle. Hold pomalidomide for a maximum of 21 days to allow for recovery. Resume treatment at same dose level.

Other ≥ grade 3 pomalidomide-related adverse events | Hold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (adverse event must resolve to ≤ grade 2).

### Pomalidomide Dose Reduction Steps

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Pomalidomide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
<td>4 mg daily on Days 1-21 every 28 days</td>
</tr>
<tr>
<td>Dose Level −1</td>
<td>3 mg daily on Days 1-21 every 28 days</td>
</tr>
<tr>
<td>Dose Level −2</td>
<td>2 mg daily on Days 1-21 every 28 days</td>
</tr>
<tr>
<td>Dose Level −3</td>
<td>1 mg daily on Days 1-21 every 28 days</td>
</tr>
</tbody>
</table>

The minimum permitted dose of pomalidomide is 1 mg.

Dose reduction for Grade 2 or Grade 3 AEs believed to be related to pomalidomide and not listed above are permitted. The AE must be documented in the CRF.
6.3 **BORTEZOMIB**

See Section 5.2. Pre-Treatment Criteria.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved.

**Instructions for Bortezomib Dose Modifications or Interruption During a Cycle.**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Grade 3 non-hematological toxicity (excluding neuropathy)</td>
<td>Withhold bortezomib until the symptoms of the toxicity have resolved; bortezomib therapy may be reinitiated at reduced bortezomib dosing by 1 dose level</td>
</tr>
<tr>
<td>≥ Grade 4 hematological toxicity</td>
<td>Withhold bortezomib until the symptoms of the toxicity have resolved, bortezomib therapy may be reinitiated at reduced bortezomib dosing by 1 dose level</td>
</tr>
<tr>
<td>Infection or viral illness</td>
<td>Day 1 of cycle. Delay cycle until infection/viral illness has resolved. Resume treatment at the same dose level. Do not dose reduce. Intra-cycle. Hold bortezomib for a maximum of 21 days to allow for recovery. Resume treatment at same dose level.</td>
</tr>
<tr>
<td>Grade 1 neuropathy without pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 neuropathy with pain or grade 2 (interfering with function but not with activities of day living)</td>
<td>Reduce by one dose level</td>
</tr>
<tr>
<td>Grade 2 neuropathy with pain or Grade 3 neuropathy</td>
<td>Withhold bortezomib until toxicity resolves ≤ grade 2, bortezomib therapy may be reinitiated at one does level reduction</td>
</tr>
<tr>
<td>Grade 4 neuropathy</td>
<td>Permanently discontinue study treatment</td>
</tr>
</tbody>
</table>

**Bortezomib Dose Reduction Levels**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Bortezomib dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>1.3 mg/m²</td>
</tr>
<tr>
<td>Dose level −1</td>
<td>1 mg/m²</td>
</tr>
<tr>
<td>Dose level −2</td>
<td>0.7 mg/m²</td>
</tr>
</tbody>
</table>

The minimum permitted dose level for bortezomib is 0.7 mg/m².

Dose re-escalation is permitted for bortezomib at the treating physician’s discretion.

6.4 **DEXAMETHASONE**

**Instructions for Dexamethasone Dose Modifications or Interruption During a Cycle**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Low Dose Dexamethasone Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia = Grade 1-2</td>
<td>Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.</td>
</tr>
<tr>
<td>Condition</td>
<td>Action</td>
</tr>
<tr>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>Dyspepsia ≥ Grade 3</td>
<td>Withhold dose until symptoms are controlled. Add H2 blocker or equivalent and decrease one dose level when dosing is resumed.</td>
</tr>
<tr>
<td>Edema ≥ Grade 3</td>
<td>Use diuretics as needed and decrease dose by one dose level.</td>
</tr>
<tr>
<td>Confusion or mood alteration ≥ Grade 2</td>
<td>Withhold dose until symptoms resolve. When dosing is resumed, decrease dose by one dose level.</td>
</tr>
<tr>
<td>Muscle weakness (steroid myopathy) ≥ Grade 2</td>
<td>Withhold dose until muscle weakness ≤ Grade 1. When dosing is resumed, decrease dose by one dose level.</td>
</tr>
<tr>
<td>Hyperglycemia ≥ Grade 3</td>
<td>Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed.</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Discontinue dexamethasone from treatment regimen.</td>
</tr>
<tr>
<td>Other ≥ Grade 3 dexamethasone-related adverse events</td>
<td>Withhold dexamethasone dosing until the adverse event resolves ≤ Grade 2. Decrease by one dose level when dosing is resumed.</td>
</tr>
</tbody>
</table>

Dose reduction for Grade 2 or Grade 3 AEs believed to be related to dexamethasone and not listed above are permitted. The AE must be documented in the CRF.

More aggressive dose reductions for lower grade toxicity than those listed above must first be discussed with the Principal Investigator.

For participants receiving elotuzumab, regardless of dexamethasone dose reduction, at least 8 mg of the weekly dexamethasone dose must be administered IV as part of the premedication for elotuzumab with the remainder of the weekly dexamethasone dose administered orally. Contact the Principal Investigator to discuss dexamethasone IV premedication for subjects who must discontinue dexamethasone due to an adverse event.

Dose escalation of dexamethasone is permitted after toxicities resolve, at the treating physician’s discretion.

### 6.4.1 Total Dexamethasone Dose Administration for Patients with None or Grade 1 Prior Infusion Reaction

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>Week with elotuzumab</th>
<th>Week without elotuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>−1</td>
<td>12 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>−2</td>
<td>0 mg</td>
<td>8 mg</td>
</tr>
</tbody>
</table>

### 6.4.2 Total Dexamethasone Dose Administration Patients with prior Grade 2 Infusion Reaction

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>Week with elotuzumab</th>
<th>Week without elotuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>40 mg</td>
<td>0 mg</td>
</tr>
<tr>
<td>−1</td>
<td>20 mg</td>
<td>0 mg</td>
</tr>
<tr>
<td>−2</td>
<td>10 mg</td>
<td>0 mg</td>
</tr>
</tbody>
</table>
6.4.3 Total Dexamethasone Dose Administration Patients with prior Grade 3 Infusion Reaction or Recurrent Grade 2 infusion reaction

<table>
<thead>
<tr>
<th>Dose levels</th>
<th>Week with elotuzumab</th>
<th>Week without elotuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PO</td>
<td>IV</td>
</tr>
<tr>
<td>0</td>
<td>8 mg (12-24 hours prior) and 8 mg (at least 3 hours prior)</td>
<td>18 mg</td>
</tr>
<tr>
<td>−1</td>
<td>12 mg</td>
<td>18 mg</td>
</tr>
<tr>
<td>−2</td>
<td>0 mg</td>
<td>18 mg</td>
</tr>
</tbody>
</table>

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 EXPECTED TOXICITIES

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting in addition to routine reporting.

7.1.1 Adverse Events List

7.1.1.1 Adverse Events List for Elotuzumab

Treatment with therapeutic monoclonal antibodies is associated with infusion reactions with variable time of onset and varying levels of incidence and severity. The key safety signal with elotuzumab is infusion reactions. As stated above, the definition of an infusion reaction for this analysis includes relevant signs and symptoms reported the day of or the day after elotuzumab infusion. The most frequent elotuzumab infusion reaction AEs regardless of causality across all Phase 1 studies included nausea, vomiting, chills, fever, flushing, dyspnea, cough, headache, dizziness, and rash. The majority of infusion reaction AEs were grade 1 or 2 and resolved with little or no treatment. There was no apparent dose relationship for infusion reaction.

First-dose elotuzumab infusion reactions and other peri-infusion AEs have been observed in approximately 59% to 89% of subjects in clinical trials prior to the use of premedications. With the use of premedications, approximately 12% of subjects may experience an infusion reaction, which may be severe in 2% of subjects. Symptoms of infusion reactions include pyrexia, nausea chest discomfort, chills, hyperhidrosis, rash, flushing hypertension, abdominal pain, periorbital edema, or muscle spasms.
Refer to the current Investigational drug brochure for elotuzumab for listings of treatment emergent adverse events

7.1.1.2  Adverse Events List for Pomalidomide

Common known potential toxicities, > 50%, in patients treated with pomalidomide:

- Bronchitis
- Upper respiratory tract infection, which may cause fever, pain, redness, and/or difficulty breathing
- Dizziness

Common known potential toxicities, > 10%, in patients treated with pomalidomide:

- Cardiovascular: Peripheral edema (23%)
- Central nervous system: Fatigue (55%), dizziness (18% to 20%), fever (19%), neuropathy (18%), headache (13%), confusion (10% to 12%), anxiety (11%)
- Dermatologic: Skin rash (22%), pruritus (15%)
- Endocrine & metabolic: Hypercalcemia (21%), hyperglycemia (12%)
- Gastrointestinal: Constipation (36%), nausea (36%), diarrhea (34%), decreased appetite (22%), vomiting (14%), weight loss (14%)
- Hematologic & oncologic: Neutropenia (50% to 52%; Grades 3/4: 43% to 47%), anemia (38%; grades 3/4: 22%), thrombocytopenia (25%; grades 3/4: 22%), leukopenia (11%; grades 3/4: 6%)
- Neuromuscular & skeletal: Back pain (32%), musculoskeletal chest pain (22%), muscle spasm (19%), arthralgia (16%), ostealgia (12%), myasthenia (12%), and musculoskeletal pain (11%)
- Renal: Increased serum creatinine (15%), renal failure (15%)
- Respiratory: Dyspnea (34%), pneumonia (23%), epistaxis (15%), cough (14%)

Less common known potential toxicities, 1-10%, in patients treated with pomalidomide:

- Cardiovascular: Thrombosis (venous thrombosis, pulmonary embolism, 3%), atrial fibrillation (2%)
- Central nervous system: Peripheral neuropathy (10%), chills (9%), insomnia (7%), pain (6%)
- Dermatologic: Xeroderma (9%), hyperhidrosis (6%)
- Endocrine & metabolic: Hypokalemia (10%), hyponatremia (10%), hypocalcemia (6%), and dehydration (5%)
- Gastrointestinal: Weight gain (1%)
- Genitourinary: Urinary tract infection (8%)
- Hematologic & oncologic: Lymphocytopenia (4%; grades 3-4: 2%), febrile neutropenia
(3% to 5%)
- Infection: Sepsis (6%)
- Neuromuscular & skeletal: Tremor (9%), limb pain (5%)
- Miscellaneous: Night sweats (5%)

Frequency not defined in patients treated with pomalidomide:
- Acute myelocytic leukemia, hyperbilirubinemia, hyperkalemia, increased serum ALT, interstitial pulmonary disease, neutropenic sepsis, pelvic pain, *Pneumocystis jiroveci* pneumonia, respiratory syncytial virus infection, urinary retention, vertigo

### 7.1.1.3 Adverse Events List for Bortezomib

Events that have occurred in > 10% of individuals treated with bortezomib:

- Fatigue
- Loss of strength
- Nausea
- Diarrhea
- Constipation
- Loss of appetite
- Nerve injury
- Vomiting
- Decreased blood counts
- Edema
- Muscle or joint pain
- Shortness of breath
- Cough
- Headache
- Rash
- Hypotension
- Shingles

Events that have occurred in < 10% of individuals treated with bortezomib:

- Congestive heart failure
- Dizziness.

Rare or less frequent events that have occurred in individuals treated with bortezomib:

- Tumor lysis syndrome (TLS)
- Hypertension
- Interstitial lung disease
• Pericarditis
• Arrhythmia
• Angioedema
• Hyponatremia
• Hypomagnesemia
• Hypophosphatemia
• Hypoglycemia
• Herpes meningoencephalitis

7.1.1.4 Adverse Events List for Dexamethasone

Events that have occurred in > 10% of individuals treated with dexamethasone:

• Increased appetite
• Weight gain
• Sleep disturbance
• Hypertension
• Fluid retention
• Ankle swelling
• Bruising
• Infection
• Mood changes
• Slow wound healing
• Depression
• Hyperglycemia, which may lead to fatigue, weight loss, excessive thirst, and frequent urination

Events that have occurred in < 10% of individuals treated with dexamethasone:

• Loss of appetite
• Muscle twitching
• Increased thirst
• Frequent urination
• Increased perspiration
• Diarrhea
• Nausea
• Headache
• Spinal fracture or fracture of bones
• Tachycardia
• Fungal infections
Events that have occurred in < 1% of individuals treated with dexamethasone:

- Blurred vision
- Personality changes
- Stomach ulcers with bleeding that may cause hematemesis
- Blood in the stool
- Abdominal pain

Other, less frequent, events that may occur in individuals treated with dexamethasone:

- Bowel perforation
- Irritation and bleeding of the esophagus
- Heart failure
- Allergic reaction that may lead to facial redness
- Shortness of breath
- Abdominal cramps
- Hypotension
- Convulsions
- Brain swelling
- Dizziness
- Cataracts
- Glaucoma and increased blood pressure in the eye
- Development of diabetes
- Pancreatic inflammation
- Abdominal swelling
- Hypokalemia
- DVT or PE
- Malaise
- Swelling and/or redness of skin
- Allergic skin reactions
- Itching
- Hirsutism
- Muscle weakness or loss of muscle mass
- Rupture of tendons
- Menstrual cycle disturbances
- Hiccups
7.2 **ADVERSE EVENT CHARACTERISTICS**

7.2.1 **CTCAE Term (AE description) and Grade**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:


7.2.2 **Adverse Event**

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AEs). The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not Related: There is not a reasonable causal relationship between study drug administration and the AE.

The term “reasonable causal relationship” means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events).

7.2.3 **Serious Adverse Events**

A Serious Adverse Event (SAE) is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see below for exceptions)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.
Potential drug-induced liver injury (DILI) is also considered an important medical event—see the DILI section below for a definition of a potential DILI event.
Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via the study drug is an SAE.
Although pregnancy, overdose, cancer and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs.

The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

7.2.3.1 Overdose
An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs to BMS.

7.2.3.2 Potential Drug-Induced Liver Injury (DILI)
Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs.

Potential drug induced liver injury is defined as
- AT (ALT or AST) elevation > 3 times institutional upper limit of normal (ULN) AND
- Total bilirubin > 2 times institutional ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

7.2.3.3 **Serious Adverse Event Collecting and Reporting**

Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should also report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

7.2.3.4 **SAE reporting to BMS**

SAEs, whether or not related to the study drug, and pregnancies must be reported to BMS within 1 business day of notification of the event. SAEs must be recorded in writing on the SAE Report Form; Pregnancies on a Pregnancy Surveillance Form. All reports should be submitted to the Coordinating Center (or monitor) at CCPO-mcgroup@partners.org. The Coordinating Site will facilitate PI review and submission of initial reports and any follow-up reports to BMS.

BMS SAE Email Address:  *Worldwide.Safety@BMS.com*
BMS SAE Fax Number:  609-818-3804

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available, and expectedness of the event. 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. 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 to the Coordinating Center (or monitor) using the same procedure used for transmitting the initial SAE report.
All SAEs should be followed to resolution or stabilization. A final report to document resolution of the SAE is required.

Note: Follow-up SAE reports should include the same investigator term(s) initially reported.

7.2.3.5 SAE Reporting to Celgene

SAEs, whether or not related to the study drug, and pregnancies or suspected pregnancies must be reported to Celgene within 1 business day of notification of the event. SAEs must be recorded in writing using a Celgene SAE form or MEDWATCH 3500A form. All report forms should be submitted to the Coordinating Center (or monitor) at CCPO-mcgroup@partners.org. The Coordinating Site will facilitate PI review and submission of initial reports and any follow-up to Celgene.

Celgene Corporation Global Drug Safety and Risk Management  
Connell Corporate Park  
300 Connell Dr. Suite 6000  
Berkeley Heights, NJ 07922  
E-mail: drugsafety@celgene.com  
Fax: (908) 673-9115

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available, and expectedness of the event. 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 and sent to the Coordinating Center (or monitor) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization. A final report to document resolution of the SAE is required.

Note: The Celgene tracking number and the institutional protocol number should be included on the SAE report (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.

7.2.4 Attribution of the AE:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.
7.3 **EXPEDITED ADVERSE EVENT REPORTING**

Investigators **must** report to the overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.3.1 **DF/HCC Expedited Reporting Guidelines**

Investigative sites within DF/HCC and DF/PCC will report SAEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report SAEs to their respective IRB according to the local IRB’s policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Coordinating Center within the timeframes detailed in the table below.

<table>
<thead>
<tr>
<th>Attribution</th>
<th>DF/HCC Reportable AEs</th>
<th>Gr. 2 &amp; 3 AE Expected</th>
<th>Gr. 2 &amp; 3 AE Unexpected</th>
<th>Gr. 4 AE Expected</th>
<th>Gr. 4 AE Unexpected</th>
<th>Gr. 5 AE Expected or Unexpected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unrelated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unlikely</strong></td>
<td>Not required</td>
<td>Not required</td>
<td>5 calendar days†</td>
<td>5 calendar days</td>
<td>24 hours‡</td>
<td></td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Definite</strong></td>
<td>Not required</td>
<td>5 calendar days</td>
<td>5 calendar days</td>
<td>5 calendar days</td>
<td>24 hours‡</td>
<td></td>
</tr>
</tbody>
</table>

†If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.

‡For participants enrolled and actively participating in the study or for AEs occurring within 30 days of the last intervention, the AE should be reported within **24 business hours** of learning of the event.

The Coordinating Center will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.4 **PREGNANCY**

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product
(elotuzumab, pomalidomide, bortezomib, and dexamethasone) will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

**BMS Reporting**

Any pregnancy that occurs in a female partner of a male study participant must be reported to BMS. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

**Celgene Reporting**

A pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the

The Investigator must immediately notify the Coordinating Center of this event via the BMS Pregnancy Surveillance Form AND the Celgene Pregnancy Initial Report Form, or approved equivalent form. Pregnancies must be reported to both BMS and Celgene as per instructions in Sections 7.2.3.4 and 7.2.3.5.

**The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.**

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported. The Site Investigator will follow the female subject until completion of the pregnancy, and must notify the Coordinating Center immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Site Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator’s knowledge of the event using the SAE Report Form, or approved equivalent form.

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 the IP should also be reported to the Coordinating Center immediately by facsimile, or other appropriate method, within 1 business day of the Site Investigator’s knowledge of the event using the SAE Report Form, or approved equivalent form.

**7.4.1 Male Subjects**

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP 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.

7.5 **EXPEDITED REPORTING TO THE FOOD AND DRUG ADMINISTRATION (FDA)**

The Overall PI, as study sponsor, with the assistance of the Coordinating Center, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA’s criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 **EXPEDITED REPORTING TO HOSPITAL RISK MANAGEMENT**

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 **ROUTINE ADVERSE EVENT REPORTING**

All Adverse Events must be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

8. **PHARMACEUTICAL INFORMATION**

A list of the adverse events and potential risks associated with the investigational and standard agents administered in this study can be found in Section 7.1.

8.1 **ELOTUZUMAB**

8.1.1 **Description**

Elotuzumab (BMS-901608; also known as HuLuc63) is a humanized recombinant monoclonal IgG1 antibody product directed to human CS1 (CD2-subset-1, also known as CRACC and SLAMF7), a cell surface glycoprotein that is highly expressed in MM cells.

Elotuzumab consists of the complementarity determining regions of the mouse antibody, MuLuc63, grafted onto human IgG1 heavy and kappa light chain framework regions.

Molecular weight is 148086.6 daltons.

It is a colorless to slightly yellow liquid, essentially free of visible particles.

Solution pH 5.7 - 6.3

Isoelectric point (pI) 8.7
8.1.2 Form

Elotuzumab for injection, 400 mg/vial.

Elotuzumab for injection has been developed to be used as an intravenous (IV) infusion for clinical studies. Drug product is a non-pyrogenic lyophilized powder which is white to off-white contained in 20-cc Type I glass vials, closed with 20-mm stoppers and sealed with aluminum seals. Each vial of drug product contains the labeled amount of BMS-901608 drug substance, sucrose, sodium citrate dihydrate, citric acid, and polysorbate 80. A 10% overfill is included in each vial to account for vial, needle, syringe (VNS) holdup. The drug product will be reconstituted prior to administration.

8.1.3 Storage and Stability

The lyophilized elotuzumab drug product should be stored at 2° to 8°C. Prior to administration the drug product must be reconstituted with sterile water for injection, USP, then further diluted in 0.9% sodium chloride normal saline, USP. After the dose is diluted in normal saline, the elotuzumab infusion must be administered within 8 hours if stored at room temperature. If a delay is anticipated, the prepared dose may be refrigerated at 2° to 8°C for up to 24 hours. If stored under refrigerated conditions, the prepared study drug solution should be equilibrated to room temperature (process takes 2-2.5 hours) and the container must be gently inverted to mix well before administration. Do not use the accelerated warming method. If administration is delayed beyond the specified time, the prepared dose solution must be discarded, and the reason documented. The dose of elotuzumab to be administered to a subject will be calculated by multiplying the patient’s weight (kg) by 10 mg/kg or 20 mg/kg.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.5 Availability

Bristol-Myers Squibb will supply elotuzumab. Elotuzumab is an investigational agent and will be supplied free-of-charge. Drug will be shipped to the pharmacy at the study site.

8.1.6 Preparation

Each vial of Elotuzumab for Injection, 400 mg/Vial should be reconstituted with sterile water for injection (SWFI) at the clinical compounding site. Prior to IV administration, the reconstituted solution is diluted with 0.9% sodium chloride injection (NS) to result in an elotuzumab concentration from 0.9 mg/mL to no higher than 6.6 mg/mL in a polyvinyl chloride or polyolefin infusion bag. Additionally, 5% dextrose injection (D5W) may be used as a diluent in place of 0.9% sodium chloride injection. The infusion is to be administered through a sterile,
non-pyrogenic, low protein binding in-line filter using an automated infusion pump. Additionally, care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain anti-microbial preservatives or bacteriostatic agents. A sufficient excess of drug product is included in each vial to account for withdrawal losses.

8.1.7 Administration

See Appendix F: Preparation and Administration of Elotuzumab.

8.1.8 Ordering

The investigator or designee will order elotuzumab from Bristol-Myers Squibb, according to the ordering instructions provided by company.

8.1.9 Accountability

The investigator or designee is responsible for taking an inventory of each shipment of elotuzumab received, and comparing it with the accompanying accountability form. The Investigator, or designee, will verify the accuracy of the information on the form, sign and date it, retain a copy in the study fill. Accurate records will be kept in the source documentation of all drug administration (including dispensing and dosing).

8.1.10 Destruction and Return

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the Site Investigator’s or designee’s responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented.

8.2 POMALIDOMIDE

8.2.1 Description

Pomalidomide, 4-amino-2-(2,6-dioxo-3-piperidyl)isoindoline-1´-one)-1,3-dione, belongs to the IMiD class of compounds. The Chemical Abstract Service (CAS) registry number for CC-4047 is 19171-19-8. The chemical structure of the active pharmaceutical ingredient (API) is as follows:

![Chemical Structure of Pomalidomide]
Pomalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S (−) and R (+). Pomalidomide is being developed as a racemate.

8.2.2 Form

Pomalidomide will be supplied as 1 mg, 2 mg, 3 mg, and 4 mg capsules for oral administration.

8.2.3 Storage and Stability

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

8.2.4 Handling

Females of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.5 Availability

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. Pomalidomide will be provided by Celgene Corporation in accordance with the 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.

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. Pomalidomide will be sent to the research pharmacy.

Female participants must follow pregnancy testing requirements as outlined in the Pomalyst REMS program.

8.2.6 Preparation

Pomalidomide is an oral drug, and does not require specific preparation details.

8.2.7 Administration

See Section 5.3. Agent Administration for details.
At all times when dispensing pomalidomide protocol therapy, study site personnel will review the instructions, printed on the packaging, with participants.

8.2.8 Ordering

See Section 8.2.5. Availability

8.2.9 Accountability

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form.

8.2.10 Destruction and Return

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

8.3 BORTEZOMIB

8.3.1 Description

Bortezomib for Injection is a small molecule proteasome inhibitor developed by Millennium as a novel agent to treat human malignancies. By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The anti-neoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. In MM, bortezomib results in the accumulation of unfolded proteins, activating the unfolded protein response.

8.3.2 Form

Bortezomib for Injection is a sterile lyophilized powder for reconstitution and is available in sterile, single use vials containing bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of bortezomib contain 35 mg of mannitol. Bortezomib is commercially available and will not be supplied as part of this clinical trial.

8.3.3 Storage and Stability

Bortezomib will be stored according to institutional practice.

8.3.4 Handling

Bortezomib is cytotoxic and handled according to institutional practice.
8.3.5 Availability

Commercial supplies of bortezomib will be used for this study.

8.3.6 Preparation

Bortezomib will be prepared according to institutional practice. Refer to Package Insert for details. Here are guidelines:

Each vial of bortezomib should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with normal (0.9%) saline, sodium chloride injection USP. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. The reconstituted solution should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. Caution should be used when calculating the reconstituting volume and the final concentration for administration.

### Reconstitution Volume and Final Concentration for Subcutaneous Administration

<table>
<thead>
<tr>
<th>Route</th>
<th>Bortezomib (mg/vial)</th>
<th>Diluent (0.9% sodium chloride)</th>
<th>Final bortezomib concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous</td>
<td>3.5 mg</td>
<td>1.4 mL</td>
<td>2.5 mg/mL</td>
</tr>
</tbody>
</table>

8.3.7 Administration

Bortezomib will be administered according to institutional practice and according to the schedule in Section 5.3: Agent Administration.

When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated. Refer to Package Insert for details.

8.3.8 Ordering

Bortezomib will be ordered from commercial supply per institutional practice.

8.3.9 Accountability

Commercial supplies of bortezomib will be used for this trial. No drug accountability records are required.
8.4 DEXAMETHASONE

8.4.1 Description

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally-occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs. The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. Dexamethasone is stable in air and almost insoluble in water. The empirical formula is C$_{22}$H$_{29}$FO$_{5}$ and the structural formula is:

![Dexamethasone Structural Formula]

8.4.2 Form

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 2 or 4 mg tablets (commercially) for oral administration.

8.4.3 Storage and Stability

Dexamethasone will be stored according to institutional practice.

8.4.4 Handling

Dexamethasone will be handled according to institutional practice.

8.4.5 Availability

Commercial supplies of dexamethasone will be used for this study.

8.4.6 Ordering

Dexamethasone will be ordered from commercial supply per institutional practice.

8.4.7 Preparation

Dexamethasone for injection will be prepared according to institutional practice.
8.4.8 Administration

Dexamethasone will be administered according to institutional practice and according to Section 5.3: Agent Administration.

8.4.9 Ordering

Commercial supplies of dexamethasone will be used for this trial.

8.4.10 Accountability

Commercial supplies of dexamethasone will be used for this trial. No drug accountability records are required

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

This trial will provide samples from patients with relapsed disease who are uniformly treated to comprehensively characterize the MM genome and transcriptome (via expression profiling and/or sequencing), to define molecular events driving progression of MM, as well as to identify novel therapeutic targets and biomarkers.

Analysis will include genotyping by the Snapshot platform at Massachusetts General Hospital.

Analysis may also include expression profiling using the MMprofiler by Skyline Dx.

One of the aims of the study is explore clonal heterogeneity and evolution and how this correlates with disease response.

The Streck tubes will be provided to each site for collection of peripheral blood and bone marrow aspirates. Sites will be responsible for the standard purple top (EDTA) and green top (heparin) tubes.

9.1 Bone Marrow Aspirate

Collection of bone marrow aspirate specimens for exploratory analysis is recommended (see also Section 10.1. Study Calendar for Research Samples). Bone marrow aspirate will be collected according to the Study Calendar. There is a ± 10 day window for obtaining these samples. Specimens will be shipped (via traceable carrier) to and subsequently processed, analyzed, and stored at Massachusetts General Hospital or with delegated investigators. Participating sites are responsible for shipment of specimens.

9.1.1 Sample Instructions

9.1.1.1 Bone Marrow Aspirate Specimens Required

At screening and subsequent time points:
- 2 purple top tubes (10 mL)
- 2 green top tubes (10 mL)
- DF/HCC sites only: 1 Streck Cyto-Chex BCT tube (purple tiger 5 mL)

Tubes may be filled roughly one third to half way with bone marrow aspirate.

Specimens must be collected on Mondays, Tuesdays, Wednesdays or Thursdays for same-day shipment.

**9.1.1.2 Processing Information**

There is no required processing for bone marrow samples at each participating site prior to shipment.

**9.2 Peripheral Blood Samples**

Please refer to the Study Calendar for timing of collection. There is a ± 10 day window for obtaining these samples. Specimens will be shipped (via traceable carrier) to and subsequently processed, analyzed, and stored at Massachusetts General Hospital or with delegated investigators. Participating sites are responsible for shipment of specimens.

**9.2.1 Sample Instructions**

**9.2.1.1 Peripheral Blood Specimens Required**

The following should be collected per Study Calendar. Specimens must be collected on Mondays, Tuesdays, Wednesdays or Thursdays for same-day shipment

- 2 purple top tubes (EDTA, 6 mL)
- 1 Streck cell-free DNA BCT tube (brown tiger 10 mL)
- DF/HCC sites only: 1 Streck Cyto-Chex BCT tube (purple tiger 5 mL)

**9.2.1.2 Processing Information**

There is no required processing for peripheral blood samples at each participating site prior to shipment.

**9.3 Shipping Instructions**

Refer to table below for shipping destination of samples.

Bone marrow and peripheral blood samples must be shipped on the day of collection and cannot be batched. All samples are shipped ambient.

Prior to shipping any samples, please notify the Coordinating Center of the pending shipment and the samples included. For sites outside of Massachusetts, ship Monday, Tuesday, Wednesday, or Thursdays as shipments cannot be received on weekends and/or on holidays.
For sites in Massachusetts, Friday sample collection is permitted provided that samples arrive by noon.

Label all specimens with the following:

- Protocol Number (15-475)
- Subject Initials
- Subject study number
- Visit at which sample was drawn (screening, cycle number and day, complete response assessment (yes/no), etc.)
- Date sample drawn (mm/dd/yyyy)
- Time sample drawn (24 hour clock)
- Type of sample

An inventory sheet including a complete list of samples shipped (patient number, time point, study #) must accompany each shipment. Please sign and date the form, and retain a copy for site record maintenance. Please send an electronic copy of the sample list by email or fax to the Coordinating Center. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.

**Bone marrow and peripheral blood correlative samples**

<table>
<thead>
<tr>
<th></th>
<th>Purple top</th>
<th>Green top</th>
<th>Streck Cyto-Chex BCT (purple tiger)</th>
<th>Streck cell-free DNA BCT tube (brown tiger)</th>
<th>Destination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All sites</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td>Lohr laboratory</td>
</tr>
<tr>
<td>Peripheral blood</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DF/HCC only</strong></td>
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<tr>
<td>Bone marrow</td>
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<td></td>
<td></td>
<td>MGH flow cytometry</td>
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<tr>
<td>Peripheral blood</td>
<td>1</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lohr laboratory**

Attention: Tushara Vijaykumar  
Dana-Farber Cancer Institute  
DA-542  
1 Jimmy Fund Way  
Boston, MA 02115  
Email: Tushara_Vijaykumar@dfci.harvard.edu  
Phone: 312-662-2799

Please alert Tushara Vijaykumar and the Coordinating Center by e-mail when samples are being sent.
**MGH flow cytometry**

Attention: David Dombkowski  
Simches 3434  
Massachusetts General Hospital  
185 Cambridge St.  
Boston, MA 02114  
Email: dombkowski@helix.mgh.harvard.edu  
Phone: 617-726-1683

Please alert David Dombkowski and the Coordinating Center by e-mail when samples are being sent.

### 10. STUDY CALENDAR

Screening evaluations are to be conducted within 21 days prior to initiation of protocol therapy. Baseline assessments are to be conducted on Cycle 1 Day 1 of treatment. If screening assessments are performed within 7 days of Cycle 1 Day 1, disease assessments do not need to be repeated. Unless otherwise specified, drug administration and assessments have a ± 3 day window. However, all assessments must be performed prior to administration of any study medication.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening</th>
<th>Cycle 1-8</th>
<th>Cycle 9+</th>
<th>End of treatment</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>Day 8</td>
<td>Day 15</td>
<td>Day 15</td>
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<tr>
<td>Inclusion/exclusion criteria</td>
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<tr>
<td>Complete medical history</td>
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<tr>
<td>Myeloma history</td>
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<td>Vital signs, height, weight, BSA</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>Physical examination</td>
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<td>Adverse events</td>
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<td>Chest X-ray</td>
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<td>Quality of life questionnaires</td>
<td>X</td>
<td>X (odd cycles)</td>
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<tr>
<td>Monoclonal protein studies and B2M</td>
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<td>X</td>
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<tr>
<td>Skeletal survey</td>
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<tr>
<td>Evaluation of soft tissue plasmacytomas</td>
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<tr>
<td>Bone marrow aspirate</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure</td>
<td>Screening a</td>
<td>Cycle 1-8</td>
<td>Cycle 9+</td>
<td>End of treatment b</td>
<td>Follow up</td>
</tr>
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<td>-----------</td>
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</tr>
<tr>
<td>and biopsy k</td>
<td></td>
<td>Day 1</td>
<td>Day 8</td>
<td>Day 15</td>
<td>Day 22*</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>X</td>
<td>X*</td>
<td>X</td>
<td>X*</td>
<td>X</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>Days 1-21</td>
<td></td>
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<td></td>
<td>Days 1-21</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Dexamethasone</td>
<td>Refer to protocol</td>
<td>Refer to protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a. Assessments required at screening visit, except for hematology, do not have to be repeated if performed ≤7 days prior to Cycle 1 Day 1 unless otherwise specified. To take into account scheduling conflicts (e.g., over public holidays), a ±3 day window will be allowed for all assessments, unless otherwise specified.
b. End of treatment visit should occur within 28 days of discontinuation of treatment.
c. Height required at baseline only. BSA to be calculation and weight will be done according to institutional practice. Note vital sign measurements as per section on elotuzumab dosing.
d. Coagulation profile includes prothrombin time (PT) or International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen. Evaluation should be performed at screening visit and may be repeated at the Investigator’s discretion, if medically indicated. If patient is receiving warfarin, then coagulation parameters should be monitored more frequently, per investigator’s discretion.
e. Chemistry includes the following parameters: complete metabolic panel (includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, AST, ALT, alkaline phosphatase, total bilirubin), as per local institutional practice, and LDH. If total bilirubin > ULN, direct and indirect bilirubin should be performed as per institutional practice.
f. Females of reproductive potential must have 2 negative pregnancy tests before initiating pomalidomide (see also Appendix C). The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing pomalidomide. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Pomalidomide must be discontinued during this evaluation. Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted on Day 1 of every cycle (or at a minimum of every 28 days), and at study treatment discontinuation. Additional pregnancy counseling may be performed; see Appendix for requirements of the Pomalyst REMS program.
g. Thyroid function includes thyroid stimulating hormone (TSH) and free T4 (thyroxine).
h. Quality of life questionnaires will be administered at screening and on day 1 of each odd cycle and at the end of treatment visit. These questionnaires include the FACT-MM (version 4) and the Hospital Anxiety and Depression Scale (HADS). See Appendix.

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i. IgG, IgA, IgM, serum protein electrophoresis and immunofixation, 24 hour urine protein electrophoresis and immunofixation, and serum free light chains as well as β2-microglobulin

j. Soft tissue plasmacytomas(s): If present, must be assessed by clinical examination and MRI or CT at screening. Assessment of the lesion(s) by MRI or CT is also required at the end of Cycle 4, at time of complete response (CR) if it is achieved, and when medically indicated during treatment. Patients who discontinue for reasons other than disease progression will have clinical examination assessment of plasmacytoma every 3 months in follow-up and until disease progression or death.

k. Bone marrow aspiration and biopsy to be evaluated for morphology and for cytogenetics by standard banding and FISH, including marrow karyotype if possible. Suggested probes include, at a minimum del 13q14, t(4:14), t(11:14), t(14:16), and del 17p. After baseline, bone marrow sampling to confirm CR and at the end of cycle 4 for all patients. See also Section 10.1. Study Calendar for Research Samples.
10.1 **STUDY CALENDAR FOR RESEARCH SAMPLES**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening</th>
<th>C3D1</th>
<th>C5D1</th>
<th>End of study or disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow aspirate</td>
<td>X</td>
<td>X*</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*May be performed earlier to confirm complete response

11. **MEASUREMENT OF EFFECT**

11.1 **DEFINITIONS**

11.1.1 **Evaluable for toxicity**

All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

11.1.2 **Evaluable for response**

All patients who receive at least one complete cycle of treatment will be included in a response evaluation. Responses will be classified according to the definitions stated below. Participants who do not complete cycle 1 (e.g. due to disease progression or who die prior to the end of cycle 1) will not be considered evaluable for response; these participants may be replaced.

11.2 **DISEASE PARAMETERS**

11.2.1 **Measurable disease**

Measurable disease is disease that can be measured either by serum, urinary evaluation of the monoclonal component, or by serum assay of FLC, and is defined by at least one of the following three measurements:

- Serum M-protein $\geq 0.5 \text{ g/dL}$
- Urine M-protein $\geq 200 \text{ mg/24 h}$
- Involved serum FLC level $\geq 100 \text{ mg/L}$, provided serum FLC ratio is abnormal

11.2.2 **Methods for Evaluation of Measurable Disease**

All baseline evaluations should be performed on Cycle 1, Day 1 of therapy. Response will be assessed by serum M-protein quantification using protein electrophoresis and immunofixation.
from serum and 24-hour urine collection and protein electrophoresis and immunofixation. Serum free light chain testing will be performed. In addition, bone marrow aspiration will be performed when indicated to confirm response and to differentiate between CR and stringent CR.

11.3 RESPONSE CRITERIA

Disease response will be assessed using the International Myeloma Working Group Response Criteria (IMWG) as updated below (Rajkumar et al., 2011). All response categories require one confirmation. Bone marrow biopsy findings do not require confirmation.

11.3.1.1 International Myeloma Working Group Response Criteria

<table>
<thead>
<tr>
<th>Response</th>
<th>IMWG criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>CR as defined below plus: Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or 2-4 color flow cytometry</td>
</tr>
<tr>
<td>CR</td>
<td>Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and &lt; 5% plasma cells in bone marrow. In patients with only FLC measurable disease, a normal FLC ratio of 0.26-1.65.</td>
</tr>
<tr>
<td>VGPR</td>
<td>Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level &lt; 100 mg/24 h. In patients with only FLC measurable disease, &gt; 90% decrease in the difference between involved and uninvolved FLC.</td>
</tr>
<tr>
<td>PR</td>
<td>≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥ 90% or to &lt; 200 mg/24 h If the serum and urine M-protein are unmeasurable* a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>Not meeting criteria for CR, VGPR, PR, or progressive disease</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>Increase of ≥ 25% from lowest response value in any one of the following: Serum M-component (the absolute increase must be ≥ 0.5 g/dL) and/or Urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or Only in patients without measurable serum and urine M-protein, the absolute increase in FLC must be &gt;10 mg/dL (100 mg/L) Only in patients without measurable serum and urine M-protein and without measurable</td>
</tr>
</tbody>
</table>
disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%)  
Definite development of new bone lesions or soft tissue plasmacytomas or definite  
increase in the size of existing bone lesions or soft tissue plasmacytomas  
Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be  
attributed solely to the plasma cell proliferative disorder

*See Section 11.2.1. Measurable disease

11.3.2 Additional response criteria for specific disease states

Adapted from Blade et al. (1998), EBMT criteria.

**Minor response**  
25-49% reduction of serum M protein and reduction in 24 hour urine M  
protein by 50-89% which still exceeds 200 mg/24 hrs.  
If present at baseline, 25-49% reduction in the size of soft tissue  
plasmacytomas is also required  
No increase in size or number of lytic bone lesions (development of  
compression fractures does not exclude response)

11.4 Duration of Response and Endpoint Definitions

**Overall survival** (OS) is defined as the time from registration to death due to any cause, or  
censored at date last known alive.

**Duration of overall response** is measured as the time from initiation of first response to first  
documentation of disease progression or death. Patients who have not progressed or died are  
censored at the date last known progression-free.

**Duration of overall complete response** is measured as the time from initiation of CR to first  
documentation of disease progression or death. Patients who have not progressed or died are  
censored at the date last known progression-free.

**Progression-free survival (PFS)** is defined as the time from randomization to the disease  
progression or death from any cause. Patients who have not progressed or died are censored at the  
date last known progression-free.

11.5 Response Review

Disease response assessments will be performed locally and by the principal investigator.  
Central review of disease response assessments is not planned for this trial.

12. Data Reporting/Regulatory Requirements

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.  
Adverse Events: List and Reporting Requirements.
12.1 **DATA REPORTING**

12.1.1 **Method**

The DF/HCC Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 **Responsibility for Data Submission**

All participating sites are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 **DATA SAFETY MONITORING**

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information (if applicable); all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 **MULTICENTER GUIDELINES**

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing and monitoring are presented in Appendix I: Data Safety and Monitoring Plan.

- The overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.
13. STATISTICAL CONSIDERATIONS

13.1 STUDY DESIGN/ENDPOINTS

The primary endpoint is to estimate the objective response rate of the elotuzumab, pomalidomide, bortezomib, and dexamethasone combination. All patients enrolled who have received at least one cycle of treatment will be evaluable for this endpoint. All participants who receive any amount of study drug will be evaluable for toxicity.

The objective response rate (complete response and partial response) and the proportion of participants with a CR (or better), VGPR, PR, or MR will be reported.

The ORR for the combination of pomalidomide, bortezomib, and dexamethasone in the MM-005 trial was 71% (Richardson et al., 2013); recently the trial results were updated and the ORR was lower, 65% (Richardson et al., 2015). The MM-005 trial included patients who had 1-4 prior lines of treatment and whose disease was not refractory to bortezomib. Given the different eligibility criteria for this proposed elo-PVD trial, patients who are refractory to both lenalidomide and bortezomib may enroll on the trial as well as patients who have had more than 4 lines of treatment. Therefore, the ORR for the null hypothesis is anticipated to be significantly less than 65% and estimated at 40%. An objective response rate of 60% will be considered promising and 40% will be considered non-promising.

Simon’s two-stage design will be used. In the first stage, 18 patients will be accrued. If there are 7 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 28 additional patients will be accrued for a total of 46 patients. The treatment will be considered promising if 23 or more responses are observed in 46 patients. The probability of concluding the treatment is effective is 0.9 assuming a true response rate of 60% and <0.10 assuming a true response rate of 40%. The probability of stopping early in the first stage if the treatment is true response rate is 40% is 0.56. With 46 patients, the maximum exact binomial 90% confidence interval width is 0.26.

Toxicity will be summarized on all patients treated. The 90% exact binomial confidence interval will be reported.

Secondary endpoints include progression-free survival (PFS) and correlative studies. PFS (defined in section 11.4) will be estimated using the Kaplan-Meier method. The clonal evolution and clonal heterogeneity will be summarized using descriptive statistics. Exploratory analyses will be performed to correlated these endpoints with response, however, it is recognized that these analyses have limited power.

13.2 SAMPLE SIZE, ACCRUAL RATE, AND STUDY DURATION

A total of 46 patients will be enrolled. We expect 2-3 years of active accrual (estimated accrual between 15-20/year). Up to an additional 6 months of follow up will be required on the last
participant accrued. The overall study duration is expected to be a maximum of 3 years, and 2 years of follow-up of patients.

Due to the small sample size for the protocol, specific accrual targets have not been set for ethnicity or gender. Women, minorities, and members of other underrepresented populations will have equal consideration for participation in this trial.

13.3 STRATIFICATION FACTORS

There are no stratification factors in this study.

13.4 INTERIM MONITORING PLAN

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

Additional information is available in the Data and Safety Monitoring Plan (DSMP) in Appendix I.

13.5 REPORTING AND EXCLUSIONS

13.5.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.5.2 Evaluation of the Primary Efficacy Endpoint

All participants included in the study who have completed one cycle of treatment will be assessed for response to treatment.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three years after the end of the study.
15. REFERENCES


## 16. APPENDIX A. PERFORMANCE STATUS CRITERIA

<table>
<thead>
<tr>
<th>ECOG Performance Status Scale</th>
<th>Karnofsky Performance Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Descriptions</td>
</tr>
<tr>
<td>0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;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.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>
17. APPENDIX B. POMALIDOMIDE PREGNANCY RISK MINIMIZATION PLAN

The following Pregnancy Risk Minimization Plan documents are included:

- Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines, and Acceptable Birth Control Methods
- Pomalidomide Education and Counseling Guidance Document
- Pomalidomide Information Sheet

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document provides the following information:
   - Potential risks to the fetus associated with pomalidomide exposure
   - Definition of Female of Childbearing Potential (FCBP)
   - Pregnancy testing requirements for patients receiving pomalidomide who are FCBP
   - Acceptable birth control methods for both female of childbearing potential and male patients receiving pomalidomide in the study
   - Requirements for counseling of all study patients receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide

2. The Pomalidomide Education and Counseling Guidance Document must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of pomalidomide study treatment. A copy of this document must be maintained in the patient records.

3. The Pomalidomide Information Sheet will be given to each patient receiving pomalidomide study therapy. The patient must read this document prior to starting pomalidomide study treatment and each time they receive a new supply of study drug.
18. APPENDIX C. POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

Pomalidomide was found to be teratogenic in a developmental study in rabbits. 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 may cause birth defects or death to an unborn baby.

Criteria for Female of Childbearing Potential (FCBP)

This protocol defines a female of childbearing potential (FCBP) as a sexually mature woman who:

1) Has not undergone a hysterectomy or bilateral oophorectomy or
2) Has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling

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

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should 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 the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The investigator must ensure that FCBP:

- Comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, pomalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):
● She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The effect of pomalidomide on spermatogenesis is not known and has not been studied. Therefore, male patients taking pomalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

● Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential

● 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 female of childbearing potential.

**Contraception**

FCBP enrolled in this protocol must agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study:

1) For at least 28 days before starting study drug;
2) While participating in the study;
3) Dose interruptions; and
4) For at least 28 days after study treatment discontinuation.

The 2 methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

**Highly effective methods:**
- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner’s vasectomy

**Additional effective methods:**
- Male condom
- Diaphragm
- Cervical cap

Because of the increased risk of venous thromboembolism (VTE) in patients with MM taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to another one of the effective methods listed above. The risk of VTE continues for 4-6 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 patients with neutropenia.
Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP, including FCBP of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female patients:

FCBP must have 2 negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female patients:

- FCBP 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 on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.

- At each visit, the Investigator must confirm with the FCBP that she is continuing to use 2 reliable methods of birth control.

- 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 study patient, study drug must be immediately discontinued.

- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to pomalidomide 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 study patient during study participation, the investigator must be notified immediately.

Additional precautions

● Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.

● Patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.

● Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.

● Only enough study drug for one cycle of therapy may be dispensed with every cycle of therapy.
19. APPENDIX D. POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT TO BE COMPLETED PRIOR TO EACH DISPENSING OF STUDY DRUG

Protocol:  15-475

Patient Name: ___________________________________________________________________
Date of Birth:____________________________________________________________________

Check the appropriate box to indicate risk category

□ Female. If female, check one

□ FCBP (Female of Childbearing Potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) 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

□ Male.

Do not dispense study drug if:

- The patient is pregnant.
- No pregnancy tests were conducted for a FCBP.
- The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].

FCBP

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to pomalidomide: 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. The teratogenic potential of pomalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking pomalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
   - That even if she has amenorrhea she must comply with advice on contraception
   - Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
Highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner’s vasectomy

Additional effective methods:

- Male condom
- Diaphragm
- Cervical cap

Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of study drug.

Frequency of pregnancy tests to be done:

- Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient’s participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
- If the patient missed a period or has unusual menstrual bleeding.
- When the patient is discontinued from the study and at Day 28 after study drug discontinuation 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 study drug discontinuation.

Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.

NEVER share study drug with anyone else.

Do not donate blood while taking study drug and for 28 days after stopping study drug.

Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.

Do not break, chew, or open study drug capsules.

Return unused study drug to the study doctor.

3. Provide Pomalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counseled the female NOT of childbearing potential regarding the following:

- Potential risk of fetal exposure to pomalidomide (Refer to item #2 in FCBP)
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
● Do not break, chew, or open study drug capsules
● Return unused study drug capsules to the study doctor.

2. Provide Pomalidomide Information Sheet to the patient.

MALE

1. I counseled the male patient regarding the following:
   ● Potential study drug fetal exposure to pomalidomide (Refer to item #2 in FCBP).
   ● To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
   ● Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant
   ● NEVER share study drug with anyone else.
   ● Do not donate blood while taking study drug and for 28 days after stopping study drug.
   ● Do not donate semen or sperm while taking study drug and for 28 days after stopping study drug.
   ● Do not break, chew, or open study drug capsules.
   ● Return unused study drug capsules to the study doctor.

2. Provide Pomalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): ________________________________ (circle applicable)
Investigator/Counselor Signature: ________________________________ (circle applicable)
Date: _____ / _____ / _____ (month/day/year)

Maintain a copy of the Education and Counseling Guidance Document in the patient’s records.
20. APPENDIX E. POMALIDOMIDE INFORMATION SHEET

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking study drug 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?

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 rabbits.

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

- Do not take study drug if you are pregnant or plan to become pregnant
- You must either not have any sexual relations with a man or use 2 reliable, separate forms of effective birth control at the same time:
  - for 28 days before starting study drug
  - while taking study drug
  - during dose interruptions of study drug
  - for 28 days after stopping study drug
- You must have pregnancy testing done at the following times:
  - within 10-14 days and again 24 hours prior to the first dose of study drug
  - weekly for the first 28 days
  - every 28 days after the first month or every 14 days if you have irregular menstrual periods
  - if you miss your period or have unusual menstrual bleeding
  - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
- Stop taking study drug if you become pregnant during treatment
  - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene.
- Do not breastfeed while taking study drug
● The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

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 the fetus in females whose male partner is receiving pomalidomide is unknown at this time.

1. Male patients (including those who have had a vasectomy) must either not have any sexual relations with a pregnant female or a female who can become pregnant, or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
   ● While you are taking study drug
   ● During dose interruptions of study drug
   ● For 28 days after you stop taking study drug

2. Male patients should not donate sperm or semen while taking study drug and for 28 days after stopping study drug.

3. 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. Your partner should call their healthcare provider immediately if they get pregnant.

All patients:

● Restrictions in sharing study drug and donating blood:
   1. Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.
   2. Do not donate blood while you take study drug and for 28 days after stopping study drug.

● Do not break, chew, or open study drug capsules.
● You will be supplied with no more than one cycle of study drug
● Return unused study drug capsules to your study doctor or nurse.
● Additional information is provided in the informed consent form and you can ask your study doctor or nurse for more information.
21. APPENDIX F. PREPARATION AND ADMINISTRATION OF ELOTUZUMAB

Dose Preparation Instructions

After dilution in normal saline, elotuzumab must be administered within 9 hours if kept at room temperature (25°C). If a delay is anticipated after the dose has been diluted in normal saline, the prepared dose (properly identified) may be refrigerated at 2°C to 8°C 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) discussed below. The dose of elotuzumab will be calculated using institutional practice in regard to weight and then added to 0.9% saline for infusion. Dose will be rounded to nearest 1 mg.

Reconstitute elotuzumab lyophilized study drug, as described in Steps 1 to 5. Each 400 mg vial contains 10% overfill for a total of 440 mg of study drug but is intended to deliver 400 mg of elotuzumab. Standard aseptic technique should be utilized.

1. Remove the flip-top from elotuzumab and Sterile Water for Injection (SWFI) vials.

2. Withdraw 17 mL of SWFI using an 18-gauge or smaller needle. Place the elotuzumab vial upright on a flat surface and insert the syringe needle into the vial through the center of the rubber stopper. Slowly inject the SWFI along the side of the vial to help prevent bubbling or foaming. Slowly remove the syringe needle out of the vial.

3. DO NOT SHAKE. Avoid prolonged or vigorous agitation. 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.

4. After the remaining solids are completely dissolved, allow the reconstituted solution to stand for 5 to 10 minutes. The final volume of the reconstituted solution is approximately 17.6 mL, for an approximate concentration of 25 mg/mL.

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.
Once the reconstitution is completed, withdraw the calculated drug volume and further dilute with normal saline into an infusion bag (see table below). Final drug volume will be calculated based on dose level and subject weight. The final elotuzumab concentration should range from 0.9 mg/L to no higher than 6.6 mg/mL in a polyvinyl chloride or polyolefin infusion bag.

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. The same subject receiving 20 mg/kg elotuzumab 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.

Additionally, care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain anti--microbial preservatives or bacteriostatic agents. A sufficient excess of drug product is included in each vial to account for withdrawal losses.

**Dose Level and Dilution**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Volume 0.9% normal saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg</td>
<td>230 mL</td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>340 mL</td>
</tr>
</tbody>
</table>

**Elotuzumab Infusion Rate**

<table>
<thead>
<tr>
<th></th>
<th>Infusion rate</th>
<th>Duration of infusion</th>
<th>Volume delivered</th>
<th>Volume remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cycle 1 Day 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 mL/min</td>
<td>30 min</td>
<td>15 mL</td>
<td>247 mL*</td>
<td></td>
</tr>
<tr>
<td>1 mL/min</td>
<td>30 min</td>
<td>30 mL</td>
<td>217 mL</td>
<td></td>
</tr>
<tr>
<td>2 mL/min</td>
<td>110 min</td>
<td>217 mL</td>
<td>0 mL</td>
<td></td>
</tr>
<tr>
<td><strong>Cycle 1 Day 8</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mL/min</td>
<td>30 min</td>
<td>90 mL</td>
<td>172 mL</td>
<td></td>
</tr>
<tr>
<td>4 mL/min</td>
<td>43 min</td>
<td>172 mL</td>
<td>0 mL</td>
<td></td>
</tr>
<tr>
<td><strong>Cycle 1 Day 15</strong> and <strong>subsequent doses</strong></td>
<td>5 mL/min</td>
<td>53 min</td>
<td>262 mL</td>
<td>0 mL</td>
</tr>
</tbody>
</table>

*Volume calculated for an 80 kg patient. Total volume varies according to the patient weight.

**Administration Instructions**

The first dose of elotuzumab will be administered following premedications to each participant as an IV infusion, using an automated infusion pump set. Refer to above table for guidelines. If the participant does not have an infusion reaction within 30 minutes, the infusion rate is
escalated. If the participant continues to tolerate the infusion well within 30 minutes, the infusion rate is further escalated. A similar escalation process will occur with subsequent doses.

If a participant experiences a Grade 2 infusion reaction, the infusion must be interrupted. Please refer to Section 5.3 for detailed information on the management of infusion reaction and reinitiation 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.

1. Administer through a low-protein-binding 0.22-micrometer 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 previously prior to elotuzumab infusion.
APPENDIX G. FACT-MM

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP1 I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP2 I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP3 Because of my physical condition, I have trouble meeting the needs of my family.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP4 I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP5 I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP6 I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP7 I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOCIAL/FAMILY WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS1 I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS2 I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS3 I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS4 My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS5 I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS6 I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Q1 Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box and go to the next section.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GS7 I am satisfied with my sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

### EMOTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>GE1</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GE2</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am satisfied with how I am coping with my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GE3</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am losing hope in the fight against my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GE4</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel nervous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GE5</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I worry about dying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GE6</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### FUNCTIONAL WELL-BEING

<table>
<thead>
<tr>
<th>GF1</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am able to work (include work at home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GF2</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>My work (include work at home) is fulfilling</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GF3</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am able to enjoy life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GF4</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GF5</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am sleeping well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GF6</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am enjoying the things I usually do for fun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GF7</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am content with the quality of my life right now</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th>ADDITIONAL CONCERNS</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have certain parts of my body where I experience pain ................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel weak all over .................................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I get tired easily .......................................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble concentrating .........................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about getting infections ....................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel discouraged about my illness ............................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Because of my illness, I have difficulty planning for the future .....................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry that I might get new symptoms of my illness ....................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have emotional ups and downs .....................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have bone pain ............................................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I need help doing my usual activities ................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble walking because of pain ........................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel fatigued ...............................................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have gained weight .....................................................................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
22. APPENDIX H. HADS SCALE

Please read each item and select the answer which comes closest to how you have been feeling, on the average, in the past week:

I feel tense or “wound up”:
- Most of the time
- A lot of the time
- From time to time, occasionally
- Not at all

I still enjoy the things I used to enjoy:
- Definitely as much
- Not quite so much
- Only a little
- Hardly at all

I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly
- Yes, but not too badly
- A little, but it doesn't worry me
- Not at all

I can laugh and see the funny side of things:
- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not at all

Worrying thoughts go through my mind:
- A great deal of the time
- A lot of the time
- From time to time, but not too often
- Only occasionally

I feel cheerful:
- Not at all
- Not often
- Sometimes
- Most of the time

I can sit at ease and feel relaxed:
- Definitely
- Usually
- Not often
- Not at all
I feel as if I am slowed down:
- Nearly all the time
- Very often
- Sometimes
- Not at all

I get a sort of frightened feeling like “butterflies” in the stomach:
- Not at all
- Occasionally
- Quite often
- Very often

I have lost interest in my appearance:
- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

I feel restless as I have to be on the move:
- Very much indeed
- Quite a lot
- Not very much
- Not at all

I look forward with enjoyment to things:
- As much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I get sudden feelings of panic:
- Very often indeed
- Quite often
- Not very often
- Not at all

I can enjoy a good book or radio or TV program:
- Often
- Sometimes
- Not often
- Very seldom
APPENDIX I

Multi-Center Data and Safety Monitoring Plan
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1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 PURPOSE

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 MULTI-CENTER DATA AND SAFETY MONITORING PLAN DEFINITIONS

**DF/HCC Multi-Center Protocol:** A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

**Lead Institution:** One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children’s Hospital (BCH), Brigham and Women’s Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

**DF/HCC Sponsor:** The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

**Participating Institution:** An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

**Coordinating Center:** The entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol.
document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

**DF/HCC Office of Data Quality:** A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

### 2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Andrew Yee, MD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial’s conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA (investigator-held IND trials), as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.
2.2 COORDINATING CENTER

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Review and approve Participating Site informed consent forms
- Conduct and document initial and ongoing protocol training
- Oversee the data collection process from Participating Institutions.
- Maintain documentation and cumulative reports of Serious Adverse Event (SAE) reports and Deviations/Violations across all sites and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out approved protocol monitoring plan either by on-site or remote monitoring.
- Maintain essential regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites, and protocol training documentation.
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 PARTICIPATING INSTITUTION

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
Register participants through the Coordinating Center prior to beginning research related activities.

Submit Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC or other sponsor requirements.

Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.

Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.

Have office space, office equipment, and internet access that meet HIPAA standards.

Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.

Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 PROTOCOL DISTRIBUTION

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 PROTOCOL REVISIONS AND CLOSURES

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution’s responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating
Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 INFORMED CONSENT REQUIREMENTS

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB DOCUMENTATION

The following must be on file with the Coordinating Center:
- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB RE-APPROVAL

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 PARTICIPANT CONFIDENTIALITY AND AUTHORIZATION STATEMENT

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any
information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information. All consent forms must be reviewed and approved by the Coordinating Center prior to submission to the IRB.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC QACT case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

All participants must be registered with DF/HCC prior to conducting any research-related procedures.

3.7.1 Participant Registration and Randomization

Please refer to protocol Section 4.0: Registration Procedures

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant’s registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions
The DF/HCC will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC requires each institution to fully comply with this requirement.

3.8 **DF/HCC Protocol Case Number**

At the time of registration, DF/HCC requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 **Protocol Deviations, Exceptions and Violations**

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms “violation”, “deviation” and “exception” to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 **Definitions**

**Protocol Deviation:** Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

**Protocol Exception:** Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

**Protocol Violation:** Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 **Reporting Procedures**

**DF/HCC Sponsor:** is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.
Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution’s IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution’s IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 SAFETY ASSESSMENTS AND TOXICITY MONITORING

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol Section 7.2.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.
3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 DATA MANAGEMENT

The DF/HCC Office of Data Quality (ODQ) develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC ODQ provides a web based training for eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being resubmitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ and distributed on a monthly basis.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol Section 8: Pharmaceutical information.

Participating Institutions should order their own agent regardless of the supplier. If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of
who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ, provides quality control oversight for the protocol.

5.1 ONGOING MONITORING OF PROTOCOL COMPLIANCE

The Participating Institutions will be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution are also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

All Non-DF/HCC site Participating Institutions will undergo on-site monitoring by the Coordinating Center within 3 months of completion of C2 for first patient; Combination on-site and remote monitoring will occur every 4-6 months thereafter with at least 1 on-site visit every 24 months. Remote monitoring may be done in lieu of on-site monitoring if no active patients are on trial. Once all site participants are off treatment and have completed the post-treatment assessment, remote monitoring will be conducted annually for confirmation of long term follow-up data. All Participating Institutions will be required to participate in monthly Coordinating Center initiated teleconferences. Once all participants are off treatment and in long-term follow-up, teleconferences will be scheduled as needed.

For remote monitoring visits, Participating Institutions will be asked to provide remote electronic medical record access to the monitor or will be required to forward de-identified copies of participants’ medical record and source documents to the Coordinating Center to aid in source data verification. The participants and CRFs to be reviewed at the visit will be communicated at least 2 weeks in advance of the scheduled monitoring visit. Source documentation can be provided to the Coordinating Center via an encrypted memory stick or via a secure file transfer system. During remote monitoring visits, the Site Specific File will be reviewed in lieu of the site regulatory binder.

On-Site Monitoring will be scheduled several weeks in advance and will be conducted over a 2-3 day period. During an on-site monitoring visit 2-4 participants will be monitored.
Source documentation verification (SDV) will be conducted by having access to participants’ complete medical record and source documents. Participating Institutions will be expected to coordinate the necessary resources for the monitor, including a desk, access to all participant medical and research records (electronic and hard copy), the regulatory binders and access to a photocopier. The Participating Institution will also be asked to assist in scheduling a pharmacy visit and a brief exit interview on the final day of the visit with the Study Coordinator and the Site investigator.

5.2 Monitoring Reports

The Coordinating Center will summarize the findings of all monitoring visits and provide a written report to the participating site within 10-15 business days. The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. For Phase II studies, sites are expected to accrue at least 3 participants annually, with the exception of rare disease groups. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

6. Auditing: Quality Assurance

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: NCI Sponsored Trials

Not applicable.

6.2 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the ODQ, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the
site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.3 AUDIT NOTIFICATION

It is the Participating Institution’s responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol upon notification of the audit. The Coordinating Center will assist the Participating Institution with audit preparation. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.4 AUDIT REPORTS

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.5 PARTICIPATING INSTITUTION PERFORMANCE

The DF/HCC Sponsor and the DFCI IRB are charged with considering the totality of an institution’s performance in considering institutional participation in the protocol.

6.5.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site’s participation if it is determined that a site is not fulfilling its responsibilities as described above.