Protocol Title

E- PRISM (Precision Intervention Smoldering Myeloma): A Phase II Trial of Combination of Elotuzumab, Lenalidomide and Dexamethasone in High-Risk Smoldering Multiple Myeloma

NCT #: NCT02279394

IRB Approval Date: 04/09/2021

Local Protocol #: *14-338*
Bristol-Myers Squibb Protocol #: CA 204-119
Celgene Protocol #: RV-CL-MM-PI-004473

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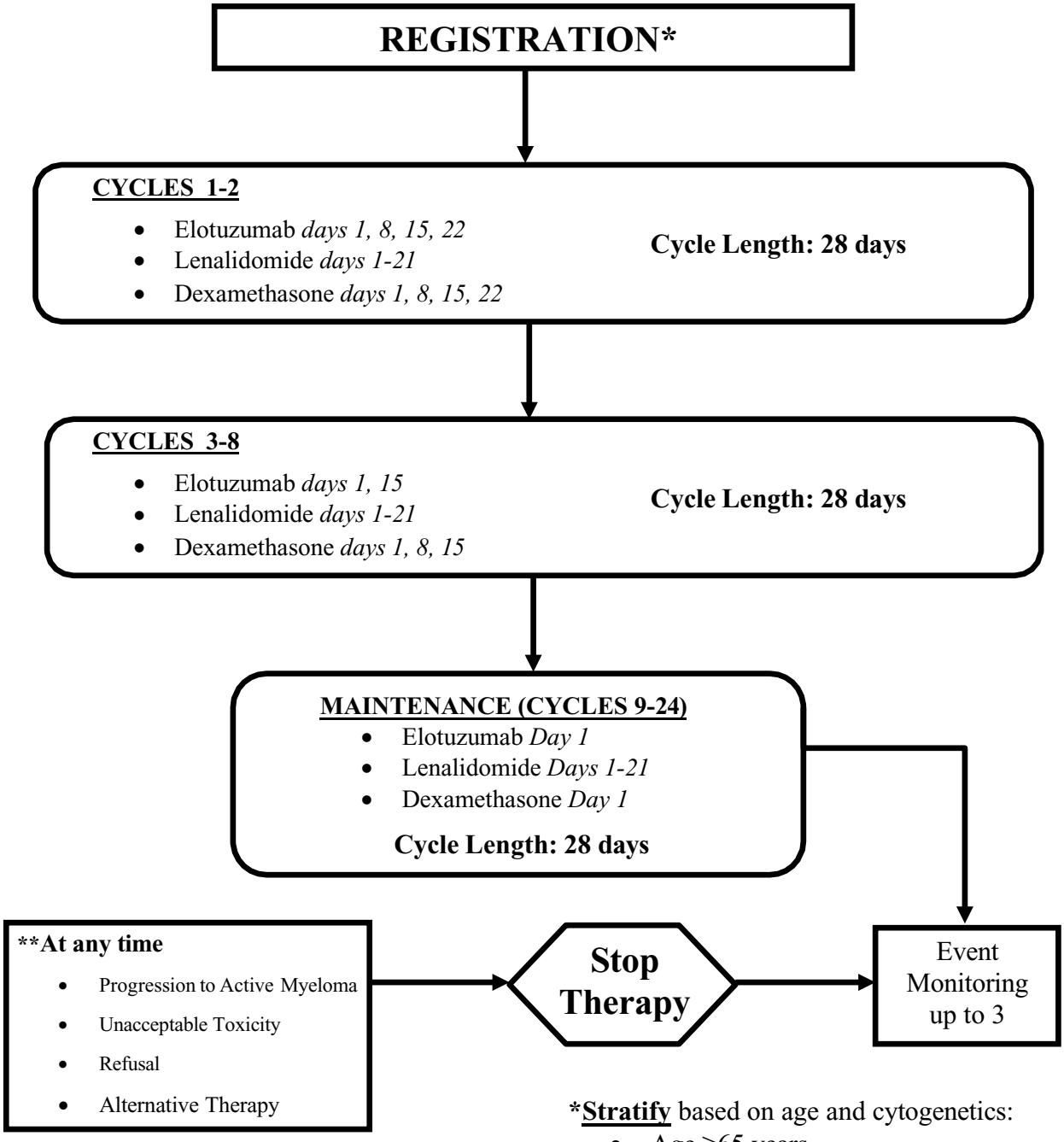
Agent(s): Elotuzumab, Bristol-Myers Squibb
Lenalidomide, Celgene
Dexamethasone, commercial

IND #: 122322

Amendment 10/ 10.0/ April 9th, 2021

SCHEMA



***Stratify** based on age and cytogenetics:

- Age ≥65 years
- High Risk Cytogenetics based on t(4:14), t(14:16), 17p deletion, or p53 mutation, and 1q amplification

****Disease Assessment**: Day 1 of each cycle

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SYNOPSIS

Study Rationale	Early therapeutic interventions in patients with smoldering MM will prevent/delay progression to overt MM. Recent studies of a phase III trial of lenalidomide and dexamethasone vs. placebo showed improved response, progression free survival and overall survival in patients with high risk SMM compared to placebo control. Therefore, there is a need to examine novel therapeutic combinations in patients with high risk smoldering MM. Based on the activity of lenalidomide and dexamethasone in patients with high risk SMM and based on the safety and activity profile of elotuzumab and lenalidomide in patients with relapsed MM, we propose to examine the activity of elotuzumab and lenalidomide in patients with high risk SMM. We will identify the role of early intervention on prevention of progression in patients with high-risk SMM who have a 50% rate of progression at 2 years.
Products	**Elotuzumab** is a humanized recombinant monoclonal IgG1 antibody product directed to human SLAMF7 (CD2-subset-1, also known as CRACC), a cell surface glycoprotein that is highly expressed in MM cells. **Lenalidomide** (REVLIMID®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. **Dexamethasone** is a synthetic adrenocortical steroid.
Study Objectives	Primary Objectives • To determine the proportion of high risk smoldering multiple myeloma patients who are progression free at 2 years after receiving elotuzumab, lenalidomide and dexamethasone combination therapy Secondary Objectives • To assess the response rate of the combination in these patients • To assess time to progression • To assess duration of response • To assess overall survival • To assess safety of the combination • To examine molecular evolution of the tumor cells • To determine the role of immune cells in the progression of smoldering MM • To determine minimal residual disease (MRD)
Efficacy Endpoints	Response will be assessed using the IMWG criteria for response in Multiple Myeloma.
Safety Endpoints	AEs will be evaluated during the treatment period using CTCAE v4.03.
Study Design	This is a phase II study using the combination of elotuzumab, lenalidomide and dexamethasone in patients with high-risk smoldering multiple myeloma.
Dosing Regimen	**Each Cycle = 28 days** **<u>Cycle 1 & 2</u>** • Elotuzumab (IV): Days 1, 8, 15 ,22 • Lenalidomide (oral): Day 1-21

	• Dexamethasone: (oral and IV): Days 1, 8, 15, 22 **<u>Cycles 3-8</u>** • Elotuzumab (IV): Days 1 and 15 • Lenalidomide (oral): Day 1-21 • Dexamethasone: (oral and IV): Days 1, 8, 15 **<u>Cycles 9-24 (maintenance)</u>** • Elotuzumab (IV): Days 1 • Lenalidomide (oral): Day 1-21
Select Inclusion Criteria	• Age ≥ 18 years. • Must have smoldering myeloma with high risk markers based on the Mayo OR the Spanish criteria and including the new criteria for SMM as described below: o Monoclonal protein in the serum of ≥ 3gm/dL and >10% plasma cells in the bone marrow with a free light chain ratio outside the range of 0.125 to 8 OR o Ratio or abnormal to normal bone marrow plasma cells greater than or equal to 95 percent or at least one immunoglobulin level lower than the normal range • No evidence of CRAB criteria or new criteria of overt MM which includes the following: o Increased calcium levels (corrected serum calcium >0.25 mmol/L (>1mg/dL) above the upper limit of normal OR >2.75 mmol/L (>11mg/dL) o Renal insufficiency (attributable to myeloma); o Anemia (Hgb 2g/dL below the lower limit of normal or <10g/dL); o Bone lesions (lytic lesions or generalized osteoporosis with compression fractures) o No evidence of the following new criteria for active MM including the following: Bone marrow plasma cells ≥60%, Serum involved/uninvolved FLC ratio ≥100, and MRI with more than one focal lesion (>5mm) • ECOG Performance Status (PS) 0, 1, or 2. (Appendix A) • The following laboratory values obtained ≤ 21days prior to registration: o ANC ≥ 1000/μL o PLT ≥ 50,000/μL o Total bilirubin ≤ 2.0 mg/dL (If total is elevated check direct and if normal patient is eligible.) o AST ≤ 3 x institutional upper limit of normal (ULN)

	○ ALT ≤ 3 x institutional upper limit of normal (ULN) • Estimated creatinine clearance ≥ 60mL/min or a creatinine ≤ 2.2 mg/dL
Select Exclusion Criteria	• Symptomatic Multiple Myeloma or any evidence of CRAB criteria. Any prior therapy for active Myeloma should also be excluded. Prior therapy for smoldering myeloma is not an exclusion criteria. Concurrent therapy with bisphosphonates are not excluded. • Other concurrent chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered investigational. Prior therapy with bisphosphonate is allowed. Prior radiation therapy to a solitary plasmacytoma is allowed. Prior clinical trials for smoldering MM or MGUS are allowed as long as the last therapy was at least 2 months prior and there was no improvement in M spike.
Study Duration	60 months

1. OBJECTIVES

The paradigm of therapy in Smoldering Multiple Myeloma (SMM) is changing as we develop better therapeutic agents that prevent end organ damage and improve survival of patients with multiple myeloma (MM)[1-3]. Indeed, recent studies of a phase III trial of lenalidomide and dexamethasone versus placebo showed improved response, progression free survival and overall survival in patients with high risk smoldering MM compared to placebo control[4]. Therefore, there is a need to examine novel therapeutic combinations in patients with high risk smoldering MM. Based on the activity of lenalidomide and dexamethasone in patients with high risk SMM and based on the safety and activity profile of elotuzumab and lenalidomide in patients with relapsed MM[5-8], we propose to examine the activity of elotuzumab and lenalidomide in patients with high risk SMM.

Pretreatment of MM cells with lenalidomide in-vitro enhances elotuzumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC) against MM cells and this has also been demonstrated in *in vivo* xenograft MM models[6]. The mechanism of synergism between these two agents has not been fully explored, however, recent discoveries into the precise mechanism of action of lenalidomide in MM has provided some insight[9]; lenalidomide-enhanced production of the cytokine interleukin-2 (IL-2), which spurs T cell production and stimulation of NK cells. The importance of the T cell mediated effect of lenalidomide has recently been elegantly demonstrated by two studies[9,10], uncovering previously unknown mechanisms of action for this drug in MM. Lenalidomide induced IL-2 production in T cells was found to be due to the depletion of two proteins, IKZF1 and IKZF3. These proteins normally function to bind the IL-2 promoter and repress IL-2 transcription in T cells, treatment with lenalidomide markedly depletes IKZF1 and IKZF3 in T cells inducing IL-2 production and T cell activation. IL-2 is known to exert anti-myeloma activity through activation of NK cells. Treatment with lenalidomide could therefore prime NK-cells for Elotuzumab-mediated ADCC, which may explain the synergistic anti-myeloma effect of these therapies. Additionally, Elotuzumab itself may activate a subset of CD8+ T cells which express EAT-2, and has been shown to bind to CD3+CD8+ T cells in blood and bone marrow from MM patients. Interestingly, both EAT-2 and CS-1 are located on chromosome 1q, this region is amplified in 30-50% of MM patients and is associated with poor prognosis and lack of response to lenalidomide plus dexamethasone. 1q amplification is known to be an early event in myelomagenesis and has been associated with an increased risk of conversion from SMM to overt MM.

Our overarching hypothesis is that early therapeutic interventions in patients with smoldering MM will prevent/delay progression to overt MM. We will examine the *in vivo* activity and safety of elotuzumab and lenalidomide in patients with high-risk SMM. We will identify the role of early intervention on prevention of progression in patients with high-risk SMM who have a 50% rate of progression at 2 years. This will be performed in a phase II study to determine progression-free survival (PFS) in this patient population. Secondary endpoints include response rate, safety of this combination in patients with high-risk SMM.

1.1 Study Design

This is a phase II study using the combination of elotuzumab, lenalidomide and dexamethasone in patients with high-risk smoldering multiple myeloma.

1.2 Primary Objectives

- To determine the proportion of high risk smoldering multiple myeloma patients who are progression free at 2 years after receiving elotuzumab, lenalidomide and dexamethasone combination therapy

1.3 Secondary Objectives

- To assess the response rate of the combination in these patients
- To assess time to progression
- To assess duration of response
- To assess overall survival
- To assess safety of the combination
- To examine molecular evolution of the tumor cells obtained
- To determine the role of immune cells in the progression of smoldering MM
- To determine minimal residual disease (MRD)

2. BACKGROUND

2.1 Multiple Myeloma

Multiple myeloma is a plasma cell neoplasm characterized by multifocal proliferation of clonal, long-lived plasma cells associated with an overproduction of monoclonal gammaglobulin [11]. In 2010 the International Myeloma Working Group (IMWG) defined monoclonal gammopathy of undetermined significance (MGUS) by the presence of serum M-protein < 3g/dL, clonal plasma cell population in the bone marrow < 10%, and the absence of end-organ damage such as hypercalcemia (serum calcium ≥ 11.5 mg/dL), renal insufficiency (serum creatinine ≥ 2 mg/dL), anemia (hemoglobin value below the lower limit of normal by more than 2 g/dL or hemoglobin value < 10 g/dL) and lytic bone lesions (CRAB features) that can be attributed to the plasma cell proliferative disorder [12]. Smoldering multiple myeloma was defined by the presence of serum M-protein ≥ 3 g/dL and/or clonal bone marrow plasma cells ≥ 10% and the absence of CRAB features clinically.

In a large population based study in Olmsted County, MN, Kyle et al. analyzed serum samples of more than 75% of residents, 50 years or older, within the county [13]. They identified MGUS in 694 of 21,463 patients tested (3.2%). While the overall prevalence was noted to be 3.2% (95 % CI, 3.0 to 3.5), there was a significant age dependent increase in both sexes with the prevalence among persons 80 years of age or older 4 times as high as among those 50-59 years of age. Age-adjusted rates were higher in men (4.0 %, 95% C.I., 3.5 to 4.4) than in women (2.7%, 95% C.I., 2.4 to 3.0). In a subsequent study on a majority of the same patients from Olmsted County, Dispenzieri, et al., used the free light chain assay (FREELITE) and showed that 0.8% of people older than 50 years had light chain-MGUS. The total MGUS prevalence including the light chain-MGUS cases was noted at 4.2% (95% C.I., 3.9 to 4.5%) [14]. A limitation of both these studies was that 97.3% of the residents of Olmsted County were white.

For SMM patients a M-protein ≥ 3 g/dL, a FLC ratio outside the range of 0.125 to 8, and ≥ 10% plasma cells in the bone marrow are considered as adverse factors in this model [15,16]. The 5-year

rate of progression in patients with 1, 2 and 3 risk factors was 25%, 51% and 76% respectively. The time to progression with these risk factors was 10, 5.1 and 1.9 years respectively. Recently Rajkumar et al. have proposed that SMM with >60% plasma cells progress to multiple myeloma within 2 years in 95% cases and should be treated at diagnosis even in the absence of symptoms [17].

Table 1: Mayo Clinic model for risk factors and % risk of progression for smoldering MM

Model	No. of risk factors	5-year progression %	Time to progression in years
Mayo Clinic model Risk factors: M-protein ≥ 3.0g/dL, ≥10% plasma cells in the BM, FLC ratio outside the range of 0.125 to 8	1	25	10
	2	51	5.1
	3	76	1.9

2.2 MGUS and SMM consistently precedes multiple myeloma

Since the early description of monoclonal gammopathy of undermined significance it was known that some cases of MGUS progressed to symptomatic myeloma, but it was not clear whether all cases of myeloma are preceded by MGUS. In a study of more than 77,000 individuals, 55 to 74 years of age, from a cancer screening trial, Landgren et al. found 71 patients who developed multiple myeloma[18]. They performed serum protein electrophoresis, immunofixation and kappa-lambda free light chain assay on prediagnostic samples in these patients. The study showed that patients who eventually developed multiple myeloma consistently had MGUS in the years preceding development of multiple myeloma. Interestingly, in half the patients, there was a steady increase in the M-protein before the development of symptomatic myeloma, while in the other half the M-protein stayed fairly stable. A second study by Weiss et al. found a monoclonal gammopathy in 27 of 30 patients (90%) in sera 2 or more years before the diagnosis of myeloma [19].

2.3 Molecular studies in MGUS and SMM

A recent study using SNP-based arrays compared MGUS, SMM and MM samples [20]. They found copy number abnormalities in all stages. The incidence of genomic imbalance did increase from a median of 5/case for MGUS to 7.5/case for SMM and 12/case for MM. The study also noted certain genomic changes that were exclusive to MM including 11q and 21q gains and 16q and 22q deletions. Interestingly, the study found these abnormalities in a small subclone in MGUS patients indicating that most if not all of the chromosomal changes may be already present at the MGUS state. These findings also support a possible role of 'clonal tides' in the evolution from precursor state to symptomatic myeloma as explained below.
Two major pathways have been proposed as the early oncogenic events in the development of the myeloma cell based on chromosomal abnormalities noted in MGUS, SMM and MM- the non-hyperdiploid and the hyperdiploid pathway. The main cytogenetic changes that have been observed in MGUS and SMM are indicated in the table below.

Table 2: Cytogenetic abnormalities in MGUS, SMM and MM

Cytogenetic abnormality	Involved oncogene	MGUS%	SMM%	MM%
IgH translocations	See below	40-50%	40-50%	50-70%
t(11;14)(q13;q32)	CCND1 (cyclin D1)	10-25%	10-25%	15%
t(4;14)(p16;q32)	FGFR3 and MMSET	2-9%	3-13%	10-15%
t(14;16)(q32;q23)	C-MAF	2-5%	2-5%	2-5%
Other IgH translocations- t(6;14)(p21;q32), t(14;20)(q32;q11) etc.	CCND3 (cyclin D3), MAFB, etc.	6-10%	1-10%	10%
13q deletion	Unknown	25-50%	35-50%	40-50%
Hyperdiploidy	Unknown	40-50%	40-50%	40-50%

Other molecular studies in MGUS and SMM included microRNA studies. MicroRNAs are single stranded RNA molecules that regulate gene expression posttranscriptionally and are being implicated in a large number of cancers [21]. A study comparing miRNA profiles of normal PC, MGUS, SMM and MM found overexpression of mir-21, mir-106~25 and mir181a and mir181b in MGUS and MM compared to normal PCs [22]. The study also found mir-32 and mir17~92 clusters to be upregulated only in MM and not in any other forms. Mir 17~92 and Mir 106~25 are known to have a role in B cell development as well as B cell lymphomas targeting PTEN, E2F1, Bcl2 and BIM [21,22]. The mir17 cluster has been shown to upregulated by the transcription factor c-Myc, which is considered a late event in myeloma progression [23-25].

With the advances in deep sequencing techniques, we are now able to study the whole genome of myeloma cells and compare that to the normal human genome. Several studies employing these techniques are beginning to shift our understanding of the pathogenesis of myeloma. These studies have revealed that the previously held dogma that cancer progression occurred through a linear cumulative acquisition of mutational changes may be too simplistic. A new model of clonal heterogeneity is beginning to emerge [26]. In fact tumor evolution may indeed proceed like Darwinian evolution with tumor progression involving a branching process with coexistent clonal heterogeneity. In this model various subclones exist in a dynamic equilibrium, competing for limited resources and over time the subclonal populations ebb and flow under environmental evolutionary pressures with alternating dominance of various subclones at different time points[27-31]. Most of these studies were done on patients with symptomatic multiple myeloma and as similar studies involving MGUS and SMM emerge, our understanding of the pathogenesis of myeloma from these precursor states will continue to evolve. It is possible that the progression from myeloma precursor state to symptomatic disease also involves 'clonal tides' with expansion of a subclone leading to progression. Several previous studies have identified clonal heterogeneity in a subset of MGUS patients[20,32,33].

2.4 Definition of SMM

The diagnosis of smoldering (asymptomatic) multiple myeloma (SMM) is based on the demonstration of M-protein in serum (>3 gm/dL) or urine and/or the presence of 10-60% clonal bone marrow plasma cells (BMPC). [1-3] The risk of progression of SMM to overt MM is approximately 10 percent per year in the first five years after diagnosis, with decreasing progression rates in later years.

But with no evidence of the following CRAB* criteria or other Myeloma defining events (MDE):

- Increased calcium levels: Corrected serum **calcium** >0.25 mmol/L(>1mg/dL) above the upper limit of normal or >2.75 mmol/L (>11mg/dL)
- **Renal** insufficiency (attributable to myeloma)
- **Anemia** (Hgb 2g/dL below the lower limit of normal or <10g/dL)
- **Bone** lesions (lytic lesions or generalized osteoporosis with compression fractures)
- Other (symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months).

*Participants with CRAB criteria that are attributable to conditions other than the disease under study may be eligible

New MDE criteria that indicates overt MM and not SMM

The following criteria are now incorporated with the CRAB criteria to indicate that patients meet criteria for therapy as symptomatic or overt MM:

- Bone marrow clonal plasma cells >60% on bone marrow examination
- Serum involved/uninvolved FLC ratio ≥100, provided the level of the involved free light chain is at least 100mg/L (a patient's "involved" free light chain- either kappa or lambda- is the one that is above the normal reference range; the uninvolved light chain is the one that typically is in, or below the normal range)*
- More than one focal lesion on MRI that is at least 5mm or greater in size

*If serum free light chain ratio is stable (not increasing) for greater or equal to six months, the patient may be eligible after discussion with the overall PI

2.5 **Definitions of high-risk SMM**

Based on the new defined high risk criteria for smoldering myeloma[2,3] as described below:

Bone marrow clonal plasma cells ≥10% and any one or more of the following:
Serum M protein ≥3.0gm/dL
IgA SMM
Immunoparesis with reduction of two uninvolved immunoglobulin isotypes
Serum involved/uninvolved free light chain ratio ≥8 (but less than 100)
Progressive increase in M protein level (Evolving type of SMM)†
Bone marrow clonal plasma cells 50-60%
Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes
t (4;14) or del 17p or 1q gain
Increased circulating plasma cells
MRI with diffuse abnormalities or 1 focal lesion (≥5mm)
PET-CT with one focal lesion (≥5mm) with increased uptake without underlying osteolytic bone destruction
Monoclonal light chain excretion of 500mg/24 hours or higher*

† Increase in serum monoclonal protein by ≥10% on two successive evaluations within a 6 month period
*Monoclonal light chain smoldering multiple myeloma[61]

2.6 **Treatment of high risk SMM**

In a randomized open-label phase 3 trial, 119 patients with high-risk smoldering myeloma were randomized to treatment or observation. Patients in the treatment group received an induction regimen (lenalidomide at a dose of 25 mg per day on days 1 to 21, plus dexamethasone at a dose of 20 mg per day on days 1 to 4 and days 12 to 15, at 4-week intervals for nine cycles), followed by a maintenance regimen (lenalidomide at a dose of 10 mg per day on days 1 to 21 of each 28-day cycle for 2 years). The primary end point was time to progression to symptomatic disease. Secondary end points were response rate, overall survival, and safety. After a median follow-up of 40 months, the median time to progression was significantly longer in the treatment group than in the observation group (median not reached vs. 21 months; hazard ratio for progression, 0.18; 95% confidence interval [CI], 0.09 to 0.32; P<0.001). The 3-year survival rate was also higher in the treatment group (94% vs. 80%; hazard ratio for death, 0.31; 95% CI, 0.10 to 0.91; P=0.03). A partial response or better was achieved in 79% of patients in the treatment group after the induction phase and in 90% during the maintenance phase. Toxic effects were mainly grade 2 or lower. Early treatment for patients with high-risk smoldering myeloma delays progression to active disease and increases overall survival. (NCT00480363).

2.7 **Elotuzumab**

Elotuzumab (HuLuc63/BMS-901608) is a humanized monoclonal IgG1 antibody product directed to human SLAMF7 (CD2 subset-1, also known as CRACC), a cell surface glycoprotein with homology to the CD2 family of cell surface proteins[34,35]. Originally, SLAMF7 was identified as a natural killer cell (NK) marker and was shown to be expressed in a subset of circulating leukocytes.10 Blood analysis confirmed expression of SLAMF7 on the cell surface of NK, NK-like T-cells (NKT), activated monocytes, CD8 positive T cells and on tissue plasma cells.11 High SLAMF7 expression was seen in plasma cells obtained from normal healthy donors and from patients with MGUS, SMM, and active MM. More than 90% of MM bone marrow samples, irrespective of cytogenetic abnormalities, express SLAMF7.. In addition SLAMF7 expression is maintained in MM subjects after relapse from therapy. A paired analysis of a subset of subjects with MM showed that SLAMF7 gene expression is detectable in subjects both at diagnosis and at relapse.

In agreement with the gene chip data, flow cytometry analysis demonstrated that CD138+ plasma cells from MM bone marrow stained strongly positive for elotuzumab binding. In addition, immunohistochemistry (IHC) using anti SLAMF7 antibodies showed strong staining of MM cells in 9/9 plasmacytoma tissue samples and in 20/20 myeloma bone marrow cores tested[36,37].

The proposed mechanism of action of elotuzumab involves natural killer (NK) cell mediated antibody dependent cell-mediated cytotoxicity (ADCC). Elotuzumab monotherapy can kill MM cell lines and primary myeloma cells in vitro in the presence of peripheral blood mononuclear cells (PBMCs) or purified NK cells. In addition, elotuzumab exhibits significant in vivo monotherapy anti-tumor activity against human myeloma xenograft models grown in severe combined immunodeficient (SCID) mice[36-38]. This in vivo anti-tumor activity of elotuzumab appears to be largely dependent on the presence of active NK cells. Experiments using an in vivo mouse xenograft model suggest that maximal antitumor activity is reached at elotuzumab serum levels of 70 to 430 mcg/mL.

2.8 **Rationale for Elotuzumab in SMM**

Although several non-clinical models demonstrated elotuzumab monotherapy activity, no objective responses were observed in subjects in Study HuLuc63-1701 (Study 1701), a Phase 1 elotuzumab monotherapy trial in humans. This is in contrast to the high response rates observed in studies of elotuzumab in combination with lenalidomide/dexamethasone (Study HuLuc-1703 (Study 1703); or bortezomib (Study HuLuc-1702 (Study 1702). The best response in Study 1701 was stable disease (SD) seen in 27% of all subjects. However, elotuzumab may have slowed disease progression in some subjects since SD was also observed in 3 subjects whose best response to prior therapy was progressive disease and some of the subjects had prolonged SD (median time to progression of 4.2 months in subjects with SD at study Day 52) suggesting possible maintenance or disease control.

Study 1701 did not completely rule out monotherapy activity for elotuzumab. Subjects in Study 1701 may have had a lower likelihood of responding to elotuzumab monotherapy due to their prior therapies, inadequate elotuzumab dosing, and host immune status. These subjects had

advanced, heavily pretreated myeloma, having received a median of 4.5 prior lines of therapy and may have been less likely to respond to any subsequent therapy. In addition, this was a Phase 1 multiple ascending dose escalation study, in which subjects were treated with potentially inadequate doses of elotuzumab. Half of the subjects received doses below the threshold required to consistently saturate bone marrow plasma cell SLAMF7and the percentage of subjects achieving SD was higher (35%) at doses adequate to saturate SLAMF7binding sites (10 and 20 mg/kg).

A primary mechanism of action of elotuzumab is NK cell mediated ADCC. In vitro, elotuzumab has no direct anti-tumor effects and requires the presence of active PBMCs or NK cells. In Study 1701, heavily pretreated subjects with advanced myeloma likely had impaired immune systems, which may also have contributed to the lack of objective responses. Host immune status is a function of both the number and intrinsic activity of specific immune cells and advanced cancers and other hematologic diseases have impaired NK cell activity. Reduced NK cell function has been reported in advanced myelodysplastic syndrome. Subjects with active myeloma have lower levels of a protein (DNAM-1) required for NK-mediated ADCC than control subjects or myeloma patients in complete response. In Study 1701, the total lymphocyte and NK cell counts in all study subjects were below the mean for healthy patients.

Subjects with earlier stages of myeloma have better NK activity and more cytotoxic NK cells. Therefore, elotuzumab may demonstrate monotherapy activity in untreated subjects in earlier stages of myeloma (e.g., prior to development of symptoms) and who are likely to have a better immune function. SMM is an appropriate patient population to test this hypothesis. Limiting enrollment to high risk SMM narrows the population to subjects in whom the risk of progression to active myeloma is higher (median time to progression of two years) and for whom chemoprevention trials are recommended.

2.9 **Rationale for dose and schedule of Elotuzumab**

In this current study, elotuzumab will be administered at 10 mg/kg per cycle. This dose intensity was chosen because it matches the dose intensity in the cohort with the higher response rate in the phase 2 portion of study 1703.

2.9.1 Non-clinical Toxicology

The expression of the elotuzumab target, SLAMF7, is restricted to malignant myeloma cells and subsets of normal leukocytes in humans (NK, NK-like T cells [NKT], activated monocytes, a subset of CD8+ T cells, and tissue plasma cells). High SLAMF7 expression was seen in plasma cells obtained from normal healthy donors and from patients with MGUS, SMM, and active MM.11 No significant expression was detected in resting CD4+ T cells, B cells, resting monocytes, neutrophils, and granulocytes. Elotuzumab binding was not observed on epithelia, vessels, or smooth muscle cells of any of the organs examined.

Elotuzumab only recognizes human SLAMF7 protein and does not appear to bind SLAMF7 from other species, including chimpanzee, cynomolgus monkey, dog, mini-pig, mouse, rabbit, rat, and rhesus monkey. Due to the lack of species-specific cross-reactivity, there are no relevant animal species in which to conduct toxicological studies. Therefore, the nonclinical studies

consisted primarily of in vitro safety assessments and in vivo biological activity assessment to address the selectivity of elotuzumab and potential toxicities.

Elotuzumab (100 and 200 mcg/mL) in vitro had no effect on lymphocytes, CD3+, CD4+, CD8+, and B cell counts in blood samples from healthy donors. NK cell counts were decreased on average by 20% at both doses of elotuzumab. The observed decline was variable between donors and ranged between 0% and 45%.

Elotuzumab at concentrations up to500 mcg/mL did not adversely affect the ability of bone marrow-derived hematopoietic stem cells to differentiate down the erythroid and myeloid pathways.

2.9.2 Clinical Experience with Elotuzumab in Multiple Myeloma

As of March 2011, the elotuzumab clinical development program has consisted of three studies in active myeloma: Study 1701, a Phase 1 elotuzumab monotherapy study; Study 1702, a Phase 1 study of elotuzumab + bortezomib; and Study 1703, a Phase 1/2 study of elotuzumab + lenalidomide/low-dose dexamethasone.

2.9.3 HuLuc63-1701, a Phase 1 Elotuzumab Monotherapy Study

In this Phase 1 study, escalating doses (0.5 - 20 mg/kg) of elotuzumab monotherapy were administered intravenously (IV) every 2 weeks for a total of 4 doses in subjects with advanced MM. Subjects with stable disease or better had the option to receive additional doses of elotuzumab. As of 03-Jul-2009, the study is complete. A total of 35 subjects were enrolled: 3 in the 0.5 mg/kg cohort, 4 in the 1.0 mg/kg cohort, 6 in the 2.5 mg/kg cohort, 4 in the 5.0 mg/kg cohort, 4 in the 10 mg/kg cohort, and 14 in the 20 mg/kg cohort. One (1) subject in the 10 mg/kg cohort did not receive study drug. The primary objective of this study was to determine the MTD.

In the 2.5 mg/kg cohort, 1 out of the first 3 subjects dosed experienced a dose-limiting toxicity of (DLT) Grade 3 increase in blood creatinine levels leading to Grade 4 acute renal failure and that cohort was then expanded to include another 3 subjects. No further DLTs occurred in the 2.5 mg/kg cohort and dosing continued up to the 20 mg/kg cohort. In the 20-mg/kg cohort, 1 out of 14 subjects experienced a DLT of Grade 3 hypersensitivity. Therefore, the MTD was not reached in this study. A total of 31 SAEs were reported in 15 subjects. Six (6) of the SAEs were assessed as related to elotuzumab which included Grade 4 acute renal failure, Grade 2 chills, Grade 2 pyrexia, Grade 3 hypersensitivity, Grade 2 bradycardia, and Grade 2 chest discomfort. The most common treatment emergent AEs (TEAE) overall during the study were chills (13 [38.2%] subjects), fatigue (13 [38.2%] subjects), pyrexia (13 [38.2%] subjects), cough (10 [29.4%] subjects), headache (10 [29.4%] subjects), and anemia (9 [26.5%] subjects). The most common treatment-related AEs were chills (11 [32.4% subjects), pyrexia (6 [17.6%] subjects), and flushing (4 [11.8% subjects). There was no apparent dose response relationship with respect to the incidence of AEs overall or treatment related TEAEs. Most TEAEs and treatment-related TEAEs were Grade 1 or Grade 2.

A secondary objective of this study was assessment for preliminary activity. Nine (9) subjects

had a best response of stable disease. Although no subject had a confirmed response, this study was 1) conducted in heavily pre-treated subjects with likely compromised immune systems (for example compromised NK cell function), and 2) did not include immune activating myeloma therapies such as lenalidomide or bortezomib.

2.9.4 HuLuc63-1702, a Phase 1 Elotuzumab + Bortezomib Study

This is a Phase 1 study of elotuzumab in combination with bortezomib (plus dexamethasone if applicable) in subjects with MM who have had 1 to 3 prior therapies. Escalating doses (2.5-20mg/kg) of elotuzumab (dosed Days 1, 11) are administered in combination with 1.3 mg/m2 bortezomib (dosed Days 1, 4, 8, 11) in a 21-day cycle. Subjects with disease progression at the end of Cycle 2 or 3 also received an oral dose of 20 mg dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each cycle thereafter.

Data are preliminary as of 25-Mar-2011, 8 subjects with relapsed and relapsed and refractory MM have been treated; 3 each at 2.5, 5, and 10 mg/kg and 19 at 20 mg/kg of elotuzumab respectively. Twenty-eight (28) subjects in the intent-to-treat (ITT) population received at least 1 dose of elotuzumab and all 28 subjects (100%) experienced at least 1 AE. No DLT was observed in the study and MTD was not established up to the planned highest dose of 20 mg/kg. There were 23 (82.1%) subjects with an elotuzumab related AE. The most common AEs (in 45% or higher, regardless of causality) include Grade 1 to 3 fatigue, diarrhea, anemia, thrombocytopenia, nausea, hyperglycemia, lymphopenia, leukopenia, neutropenia, constipation, and peripheral neuropathy.

Grade 3 or higher AEs occurred in 22 (78.6%) subjects of whom 7 (25%) subjects experienced Grade 3 or higher AEs assessed as related to elotuzumab (lymphopenia, thrombocytopenia, gastroenteritis, chest pain, fatigue, and hypersensitivity). SAEs occurred in 10 (35.7%) subjects.

Additionally, 6 (21.4%) subjects, 2 in the 5.0 mg/kg and 4 in the 20.0 mg/kg cohorts, withdrew from treatment due to an AE (neuropathy peripheral (2 subjects), acute myocardial infarction, gastroenteritis, sepsis and pain in extremity). No deaths have been reported due to AEs. Overall there does not appear to be a dose relationship with the incidence of AEs.

As of 25-Mar-2011, the best clinical response (≥minimal (minor) response (MR)) and the best response rate (≥partial response (PR)) by the combined European Group for Blood and Marrow Transplantation and uniform criteria33 in 27 response evaluable subjects compare favorably to the historical, Phase 3 clinical trial of bortezomib monotherapy (APEX) in a similar population.34 The clinical response rate was 63% in Study 1702 compared to 46% in APEX and the objective response rate was 48% in Study 1702 compared to 38% in APEX. Finally, the median time to progression (TTP) was 9.5 months compared to 6.2 months in APEX.

2.9.5 HuLuc63-1703, a Phase 1/2 Lenalidomide/dexamethasone + Elotuzumab (LdE) Study

2.9.5.1 Phase 1

This is a Phase 1/2 study of elotuzumab with lenalidomide and low dose dexamethasone (Ld) in subjects with MM who have had 1 or more prior therapies. Data are preliminary as of 25-Mar-

2011. Escalating doses (5-20 mg/kg) of elotuzumab (dosed weekly in the first 2 cycles) are administered with 25 mg lenalidomide (dosed orally Days 1 - 21) and 40 mg dexamethasone (dosed orally on Days 1, 8, 15, and 22) in a 28 day cycle.

A total of 28 subjects received elotuzumab. One (1) subject was withdrawn from the study prior to receiving study drug due to investigator decision. Subjects had a median of 3 prior MM treatments. Three (3) subjects each received 5 mg/kg and 10 mg/kg and 22 subjects received 20 mg/kg of elotuzumab.

No DLT was observed during dose-escalation and an MTD was not established. The interim safety analysis revealed a key safety signal of elotuzumab-associated infusion reactions. These AEs included mostly Grade 1 and 2 nausea, dyspnea, chills, and headache. Two (2) subjects in the 20 mg/kg cohort discontinued due to infusion reactions, one Grade 4 SAE of anaphylaxis (related to elotuzumab) and one Grade 3 SAE of stridor (related to elotuzumab/dexamethasone). Subsequent to these events, a new elotuzumab premedication regimen for the whole program has been instituted to minimize infusion reactions.

The final data of this trial was published in 2012 [36]. Three cohorts were enrolled and treated with elotuzumab (5.0, 10, or 20 mg/kg intravenously) on days 1, 8, 15, and 22 of a 28-day cycle in the first two cycles, and days 1 and 15 of each subsequent cycle; lenalidomide 25 mg orally [PO] on days 1 to 21; and dexamethasone 40 mg PO weekly. Dose-limiting toxicities (DLTs) were assessed during cycle 1 of each cohort, and clinical responses were evaluated during each cycle. The first five patients received up to six cycles of therapy; subsequent patients were treated until disease progression.

Twenty-nine patients with advanced MM and a median of three prior MM therapies were enrolled; 28 patients were treated, three each in the 5.0-mg/kg and 10-mg/kg cohorts and 22 in the 20-mg/kg cohort. No DLTs were observed up to the maximum proposed dose of 20 mg/kg. The most frequent grade 3 to 4 toxicities were neutropenia (36%) and thrombocytopenia (21%). Two patients experienced a serious infusion reaction (one grade 4 anaphylactic reaction and one grade 3 stridor) during the first treatment cycle. Objective responses were obtained in 82% (23 of 28) of treated patients. After a median of 16.4 months follow-up, the median time to progression was not reached for patients in the 20-mg/kg cohort who were treated until disease progression.

2.9.5.2 Phase 2

Study 1703 is continuing in Phase 2 where subjects who have not been previously exposed to lenalidomide are randomized to 10 vs 20 mg/kg elotuzumab + Ld. Data are preliminary as of 25-Mar-2011. A total of 73 subjects with a median age of 63 years were enrolled in the Phase 2 portion; 36 subjects received 10 mg/kg elotuzumab and 37 received 20 mg/kg. In all subjects, the median number of cycles of therapy to date is 10. At least 1 AE was experienced by 100% of subjects across both dose groups, with largely similar AE rates; there were some exceptions based on preferred terms, but are not considered statistically significant or clinically meaningful.

Grade 3/4 AEs, regardless of causality occurred in 68% of subjects, which were also similar between the 2 arms (Table 1.4.2.3-1), and comparable to historical AE data for LD with lymphopenia (16%), neutropenia (14%), thrombocytopenia (15%), and anemia (10%) being most

common overall. SAEs were reported in 41% of all subjects of which 6 (8.2%) were assessed as drug related. Related SAEs included 1 subject with Grade 3 febrile neutropenia and Grade 4 neutropenia; 1 subject with Grade 3 visceral leishmaniasis, Grade 4 leukopenia, and Grade 4 thrombocytopenia; 1 subject with Grade 3 bronchitis; 1 subject with Grade 4 increased C - reactive protein and Grade 3 hyperuricemia; 1 subject with Grade 4 H1N1 influenza; and 1 subject with Grade 3 nausea. A total of 25 subjects have discontinued treatment as of the cutoff date: 9 for adverse events, 9 for disease progression, 4 for subject's decision, 2 for investigators decision, and 1 to start a new therapy.

As with prior elotuzumab studies, the interim safety analysis revealed a key safety signal of elotuzumab-associated infusion reactions defined for the purposes of these studies to include a pre-specified set of AEs that occurred on the day of, or the day after, elotuzumab infusion. Rates of infusion reactions were similar between arms with 56.2% subjects experiencing at least one infusion associated AE. All subjects have received a premedication regimen instituted at the end of Phase 1. Common infusion-associated AEs in Phase 2 included mostly Grade 1 and 2 nausea (16.4%), dizziness (11%), headache (12.3%), pyrexia (13.7%), and cough (8.2%). There was only Grade 3 infusion associated reaction: rash in a subject at 10 mg/kg.

Of the 73 treated subjects in the Phase 2 portion of this study, as of this data cut, all were randomized ≥12 weeks months prior to the cutoff date and are considered evaluable for response assessment by IMWG criteria. The ORR (≥ PR) in these 73 subjects was 82.2%. This ORR compares favorably with other Ld clinical trials in relapsed/refractory myeloma (60% ORR for LD in MM-009/010 and previously untreated myeloma (70% ORR for Ld in E4A03).

Although the study is not complete, the interim data analysis demonstrates 91.7% ORR at 10 mg/kg arm and 73.0% ORR at 20 mg/kg arm. This ORR is based on a median of 10 cycles.

Responses were rapid, with a median time to response of approximately 1 month in evaluable subjects.

2.9.5.3 Infusion Reactions

Treatment with therapeutic monoclonal antibodies is associated with infusion reactions with variable time of onset and varying levels of incidence and severity. As of March 2011 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.

To minimize infusion reactions, all ongoing elotuzumab studies were amended in 2010, after the Grade 3 infusion AEs in the Phase 1 program (1701, 1702, and 1703Ph1), to ensure that all subjects receive premedication with IV corticosteroids, oral or IV diphenhydramine and oral acetaminophen prior to each elotuzumab infusion. As of 25-Mar-2011 all subjects treated in the Phase 2 expansion of Study 1703 have received this amended premedication regimen. Of the 73

treated subjects, 56% of subjects experienced at least 1 Grade 1/2 infusion associated AE either the day of or the day after elotuzumab infusion. In contrast, 89% of subjects in the Phase 1 of Study 1703 (prior to new pre-medication regimen) experienced at least 1 infusion associated AE regardless of causality. Most infusion reactions occurred during the first cycle of therapy.

In summary, elotuzumab infusions have been associated with predominantly Grade 1 or 2 infusion reactions. All infusion reactions were managed by infusion rate changes and/or medications and almost all resolved the same day or within 24 hours. In most cases, subjects have been able to continue on study. Only 1 subject premedicated with diphenhydramine, acetaminophen, and IV corticosteroids prior to all doses of elotuzumab developed a Grade 3 infusion reaction related to elotuzumab and discontinued.

2.9.5.4 Clinical Pharmacokinetics

Blood samples were collected for estimation of serum elotuzumab concentrations following single and multiple dose administration in Studies 1701, 1702, and 1703. Preliminary pharmacokinetic (PK) analysis results limited to C_{min} and C_{max} have been reported for all 3 of these studies.

Following single dose administration (Study 1701) of escalating doses of elotuzumab alone, C_{max} increased with increasing dose over the dose range of 0.5 to 20 mg/kg. Following multiple dose administration of escalating doses of elotuzumab on Days 1 and 11 of a 21-day cycle in combination with bortezomib (Study 1702), the observed steady-state C_{min} values consistently remained above 70 µg/mL, the minimum maximally efficacious trough concentration, following administration of the 10 mg/kg dose (296 to 698 µg/mL) and the 20 mg/kg dose (572 to 1092 µg/mL). Following administration of elotuzumab every 7 days for the first 2 cycles, and every 14 days for all subsequent cycles in combination with lenalidomide and dexamethasone (Study 1703), the steady state C_{min} concentrations associated with the 10 mg/kg dose ranged from 163 to 301 µg/mL, which was above the minimum maximally efficacious trough concentration.

2.9.5.5 Overall Risk/Benefit Assessment

Elotuzumab is a humanized monoclonal IgG1 antibody directed to human SLAMF7, a cell surface glycoprotein. SLAMF7 is expressed on plasma cells and a subset of circulating leukocytes. Since elotuzumab does not recognize non-human SLAMF7, minimal animal toxicology has been performed. Non-clinical activity as monotherapy as well as in combination led to human trials. Although as monotherapy in heavily pretreated subject the best responses were SD, elotuzumab showed high response rates in combination with bortezomib or lenalidomide.

Elotuzumab as monotherapy or with bortezomib or lenalidomide is well tolerated. As of March 2011 the key elotuzumab related serious AEs have been infusion-related AEs.

2.10 **Trial Rationale**

Pretreatment of MM cells with lenalidomide in-vitro enhances elotuzumab induced ADCC against MM cells, and this has also been demonstrated in in vivo xenograft MM models[37]. The

mechanism of synergism between these two agents has not been fully explored, however, recent discoveries into the precise mechanism of action of lenalidomide in MM has provided some insight; lenalidomide enhanced production of the cytokine interleukin-2 (IL-2), which spurs T cell production and stimulation of NK cells. The importance of the T cell mediated effect of lenalidomide has recently been elegantly demonstrated by two studies[10,39], uncovering previously unknown mechanisms of action for this drug in MM. Lenalidomide induced IL-2 production in T cells was found to be due to the depletion of two proteins, IKZF1 and IKZF3. These proteins normally function to bind the IL-2 promotor and repress IL-2 transcription in T cells, treatment with lenalidomide markedly depletes IKZF1 and IKZF3 in T cells inducing IL-2 production and T cell activation. IL-2 is known to exert anti-myeloma activity through activation of NK cells. Treatment with lenalidomide could therefore prime NK-cells for Elotuzumab-mediated ADCC, which may explain the synergistic anti-myeloma effect of these therapies. The evidence for elotuzumab activation of immune system is based on SLAMF7 on NK cells (where EAT-2 is expressed). Interestingly, both EAT-2 and SLAMF7 are located on chromosome 1q, this region is amplified in 30-50% of MM patients and is associated with poor prognosis and lack of response to lenalidomide plus dexamethasone. 1q amplification is known to be an early event in myelomagenesis and has been associated with an increased risk of conversion from SMM to overt MM.

We will be using lenalidomide for only two years and not for longer time periods. In addition, patients who develop symptomatic disease will receive induction therapy with standard therapeutic options for multiple myeloma including combinations such as those of proteasome inhibitors, immunomodulators and steroids or cyclophosphamide, proteasome inhibitors and dexamethasone. If we observe any problems with stem cell collection, we will follow the current standard guidelines of using cyclophosphamide or plerixafor mobilization. Based on data using combination therapies for induction, there has been no major concerns regarding stem cell collections after treatment with those agents.

2.11 **Correlative Studies Background**

2.11.1 Clonal evolution in MM

The "clonal evolution" model of cancer emerged amid ongoing advances in technology, especially in recent years, during which next generation sequencing has provided ever higher resolution pictures of the genetic changes in cancer cells and heterogeneity in tumors where tumor progression proceeds in a branching rather than in a linear manner, leading to substantial clonal diversity and coexistence of wide genetic heterogeneity[40,41]. The genomic complexity in MM was recently corroborated by massive parallel-sequencing studies displaying the lack of a universal driving mutation[26]. Recent studies have shown intraclonal heterogeneity that occurs at different stages of progression in MM[27,28]. Most recently, exome sequencing confirmed that the heterogeneity observed in the transformation from MGUS/SMM to MM is likely to be an essential feature of clonal evolution and disease progression[42,43]. Point mutations such as N-RAS, K-RAS, MYC up-regulation[44], and gain or loss of chromosome 1q or 1p seem to correlate with disease progression from MGUS and SMM[25]. A progressive increase in the incidence of copy number abnormalities from MGUS to SMM and to MM has been recently observed[45].

2.11.2 Immune cells and MM

An important step in the progression of tumors is evasion and suppression of the host immune system[46,47]. Several numerical and functional T cell abnormalities have been reported in MM[48]. Studies have shown an increase of functional T-regs in MM patients and MM mouse models, which may lead to suppression of immune effector cells[49,50]. It was also reported that T-regs increase during progression in MM, and increased number of T-regs are associated with survival. Since, there are some conflicting data[8] and lack of good murine myeloma models for analyzing immune cells, the significance of T-regs and other immune cells in MM pathogenesis is not fully understood. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous, immature myeloid cell population with the ability to suppress immune responses. Recent studies have shown that MDSCs induce MM growth while suppressing T-cell-mediated immune responses. SLAMF7 is highly expressed on NK cells. Accumulating evidence indicates that EAT-2 mediates its activating effect on NK cells via tyrosine 127 which is believed to undergo phosphorylation on engagement of SLAMF7. Elotuzumab may interfere with the ability of myeloid derived suppressor cells (MDSC's) to suppress anti-myeloma immune responses by T cells or other immune cells, In mice it has been demonstrated that engagement of SLAMF7 on T helper cells inhibited antigen induced T cell proliferation and cytokine production[51], indicating that SLAMF7 may be inhibitory in T-cells however this would depend on the presence or absence of EAT2. Therefore the characterization of SLAMF7, EAT2 and elotuzumab treatment on T cell subsets remains an unanswered question in MM and may help to unravel the mechanism of synergy between elotuzumab and lenalidomide. Based on these studies and based on the SLAMF7 role in these cells, we will focus our studies of immune regulation on 3 types of cells: NK cells, T-regs and MDSCS.

3. PARTICIPANT SELECTION

3.1 **Eligibility Criteria**

3.1.1 Age ≥ 18 years.

3.1.2 Must meet criteria of high risk smoldering MM as described with one of the below criteria:

- Bone marrow clonal plasma cells ≥10% and any one or more of the following:
    - Serum M protein ≥3.0 gm/dL
    - IgA SMM
    - Immunoparesis with reduction of two uninvolved immunoglobulin isotypes
    - Serum involved/uninvolved free light chain ratio ≥8 (but less than 100)
        - *Free Light Chain Smoldering Myeloma patients as defined in section 2.4 are not excluded*
    - Progressive increase in M protein level (Evolving type of SMM)†
    - Bone marrow clonal plasma cells 50-60%
    - Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved

immunoglobulin isotypes

** All patients should have four or six color flow cytometry performed on the baseline bone marrow sample, as feasible. Patients evaluated for eligibility by Spanish Criteria must have their result confirmed by four color flow cytometry. If four or six color flow cytometry is not available at the site, the baseline bone marrow must be sent to Dana-Farber Cancer Institute to confirm eligibility prior to enrollment.*

- t (4;14) or del 17p or 1q gain
- Increased circulating plasma cells
- MRI with diffuse abnormalities or 1 focal lesion (≥5mm)
- PET-CT with one focal lesion (≥5mm) with increased uptake without underlying osteolytic bone destruction

† Increase in serum monoclonal protein by ≥10% on two successive evaluations within a 6 month period

3.1.3 No evidence of CRAB criteria* or new criteria of active MM which including the following:

- Increased calcium levels: Corrected serum calcium >0.25 mmol/L (>1mg/dL) above the upper limit of normal or >2.75 mmol/L (>11mg/dL);
- Renal insufficiency (attributable to myeloma);
- Anemia (Hgb 2g/dL below the lower limit of normal or <10g/dL);
- Bone lesions (lytic lesions or generalized osteoporosis with compression fractures)
- No evidence of the following new criteria for active MM including the following: Bone marrow plasma cells >60%, Serum involved/uninvolved FLC ratio ≥100, and MRI with more than one focal lesion

** Participants with CRAB criteria that are attributable to conditions other than the disease under study may be eligible*

3.1.4 ECOG Performance Status (PS) 0, 1, or 2 (Appendix A)

3.1.5 The following laboratory values obtained ≤ 21 days prior to registration:

- ANC ≥ 1000/μL
- PLT ≥ 50,000/μL
- Total bilirubin ≤ 2.0 mg/dL (If total is elevated check direct and if normal patient is eligible.)
- AST ≤ 3 x institutional upper limit of normal (ULN)
- ALT ≤ 3 x institutional upper limit of normal (ULN)
- Estimated creatinine clearance ≥ 60mL/min or a creatinine ≤ 2.2 mg/dL

3.1.6 Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

3.1.7 Females of childbearing potential* must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS®) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide.

** A female of childbearing potential is a sexually mature female who:*

- *has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or*
- *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 during the preceding 24 consecutive months)*

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

3.1.9 Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

3.1.10 Men must agree to use a latex condom during sexual contact with a female of childbearing potential even if they have had a successful vasectomy.

3.1.11 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Symptomatic Multiple Myeloma or any evidence of CRAB criteria including the new criteria for overt myeloma. Any prior therapy for active Myeloma should also be excluded. Prior therapy for smoldering myeloma is not an exclusion criterion. Bisphosphonates are not excluded

3.2.2 Other concurrent chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered investigational. Prior therapy with bisphosphonate is allowed. Prior radiation therapy to a solitary plasmacytoma is allowed. Prior clinical trials or therapy for smoldering MM or MGUS are allowed but should be discussed with the Principal Investigator.

3.2.3 Serious medical or psychiatric illness likely to interfere with participation in this clinical study.

3.2.4 Diagnosed or treated for another malignancy within 2 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.

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

3.2.6 Pregnant or nursing women will be excluded from the study because lenalidomide is an agent with the potential for teratogenic or abortifacient effects.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to elotuzumab or lenalidomide.

3.2.8 Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of hepatitis B virus vaccine are eligible. Patients who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.

3.3 Inclusion of Women and Minorities

3.3.1 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 DFCI by the Study Coordinator. All sites should call the Research Project Manager, at the lead site.

Following registration, participants should begin protocol therapy as soon as possible. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The lead study team should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and e-mailed to the Research Project Manager:

- Copy of labs and clinical information that satisfy inclusion criteria
- Signed participant consent form
- HIPAA authorization form
- Registration Form
- Completed eligibility checklist

The research nurse or data manager at the participating site will then call or e-mail the Research Project Manager to verify eligibility. To complete the registration process, the Research Project Manager 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. The lead site will then fax or email the participant study number to confirm registration.

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

NOTE: Registration and randomization can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC.

5. TREATMENT PLAN

5.1 Treatment Regimen

All patients will be treated with elotuzumab, lenalidomide and dexamethasone. Patients will also by stratified by age>65 years or older and high risk cytogenetics based on t(4:14), t(14:16), 17p deletion or p53 mutation, +1q amplification.

A treatment cycle is defined as 28 consecutive days.

Elotuzumab will be administered Cycles 1 and 2 on days 1, 8, 15, 22 and cycles 3-8 on days 1 and 15. Lenalidomide will be administered days 1-21 every 28 days. Dexamethasone will be administered on days 1, 8, 15 and 22 on cycles 1-2 then on days 1, 8 and 15 on cycles 3-8. Patients on maintenance treatment will be administered elotuzumab on day 1, and lenalidomide on days 1-21. For treatment cycles 1 and 2, a +/- 3 day window is allowed.

For treatment cycle 3-24, a +/-7 day window is allowed. Treatment will be administered on an *outpatient* basis.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The participant will be requested to maintain a medication diary of each dose of lenalidomide and dexamethasone. The medication diary should be returned to clinic staff at the end of each cycle.

Elotuzumab and Lenalidomide Dexamethasone Combination (Cycles 1-2)					
Agent	***Premedication and Precautions***	***Schedule***	***Dose***	***Route***	***Cycle Length***
Elotuzumab	*Premedications are described below*	*Days 1, 8, 15, 22*	*10 mg/kg*	*Intravenous-See appendix B for more details*	*28 days (4 weeks)*
Lenalidomide	*None*	*Days 1-21 of each cycle*	*25 mg*	*Oral*	
Dexamethasone	*Take with food; recommended to be taken in the morning*	*Days 1, 8, 15, 22*	*8 mg*	*IV*	
			32 mg	*Oral*	

Elotuzumab and Lenalidomide Dexamethasone Combination (Cycles 3-8)					
Agent	***Premedication and Precautions***	***Schedule***	***Dose***	***Route***	***Cycle Length***
Elotuzumab	*Premedications are described below*	*Days 1 and 15*	*10 mg/kg*	*Intravenous- See appendix B for more details*	*28 days (4 weeks)*
Lenalidomide	*None*	*Days 1-21 of each cycle*	*25 mg*	*Oral*	
Dexamethasone	*Take with food; recommended to be taken in the morning*	*Days 1, 15*	*8 mg*	*IV*	
			32 mg	*Oral*	
		Day 8	*40mg*	*Oral*	

Elotuzumab and Lenalidomide Maintenance Therapy (Cycles 9-24)					
Agent	***Premedication and Precautions***	***Schedule***	***Dose***	***Route***	***Cycle Length***
Elotuzumab	*Premedications are described below*	*Days 1 of each cycle*	*20 mg/kg*	*Intravenous-See appendix B for more details*	*28 days (4 weeks)*
Lenalidomide	*None*	*Days 1-21 of each cycle*	*15 mg*	*Oral*	
*Dexamethasone**	*Take with food; recommended to be taken in the morning*	*Day 1 of each cycle*	*8 mg*	*IV*	
			28 mg	*Oral*	

* After discussion with the overall PI, high-dose dexamethasone may be re-added during maintenance due to biochemical progression (progressive increase in SPEP [25% and an absolute increase of 0.5g/d] or UPEP [25% and an absolute increase of 200mg/24hours] on 2 successive evaluations as determined by the IMWG response criteria or documented progression by the FreeLite™ progressive disease criteria in the absence of serum or urine involvement). Dexamethasone should be given as follows after overall PI approval:

Day	**Dose**	**Route**
1	8 mg	IV
	32 mg	Oral
8	40 mg	Oral
15	40 mg	Oral

5.2 **Pre-Treatment Criteria**

There are no pretreatment criteria for elotuzumab dosing. Refer to section 6.2 for Lenalidomide pretreatment criteria and 6.3 for Dexamethasone pre treatment criteria.

5.2.1 Premedication Regimen in Subjects without a Prior Infusion Reaction

- Premedication is required prior to all Elotuzumab infusions. Refer to table 3 for the guidelines for premedication.

5.2.2 Premedication Regimen in Subjects With a Prior Infusion Reaction

To be re-treated with elotuzumab, subjects with a prior infusion reaction must receive H1, H2 blockers and acetaminophen at maximum doses specified (e.g., 50 mg diphenhydramine, 50 mg ranitidine [or equivalent], and 1000 mg acetaminophen) 90-45 minutes before initiating the elotuzumab.

Doses of intravenous dexamethasone above 10 mg require a decrease in the oral dexamethasone. Recommended dexamethasone dosing is summarized below and in Table 3.

For subjects with prior Grade 2 infusion reaction, administer 10 mg IV dexamethasone (instead of 8 mg IV) as the premedication steroid 90-45 minutes before elotuzumab. Subjects should take 30 mg oral dexamethasone 24-3 hours before elotuzumab administration.

For subjects with Grade 3 or recurrent Grade 2 elotuzumab infusion reactions, consultation with the Principal Investigator is recommended. Administer 18 mg IV dexamethasone as the premedication steroid at least 45 minutes before elotuzumab. These patients should receive 8mg of oral dexamethasone 24-12 hours the day prior to elotuzumab administration. Then, administer 14 mg oral dexamethasone at most 3 hours prior to elotuzumab administration.

If a subject with a prior Grade 2 (recurrent) or 3 infusion reaction also requires dose reduction of oral dexamethasone, the dexamethasone dose on the days of elotuzumab infusion should be no less than 18 mg IV (on the day of elotuzumab infusion at least 45 minutes before elotuzumab).

Subjects with a Grade 4 infusion reaction are not eligible to receive additional elotuzumab. These subjects may continue to receive lenalidomide and dexamethasone. Subjects who experience an infusion reaction of any grade should be administered the recommended premedication for that reaction severity for the duration of the trial.

Subjects with prior infusion reactions may receive more aggressive pre-medications after discussion with the Overall Principal Investigator

Table 3: Recommended Corticosteroid Premedication

None or Grade 1 Prior Infusion Reaction	24-3 hours prior to Elotuzumab Infusion	32 mg PO Dexamethasone
	90-45 min prior to Elotuzumab Infusion	8mg IV Dexamethasone Diphenhydramine 25-50 mg IV or PO or equivalent H1 blocker Ranitidine 50mg IV or equivalent H2 blocker Acetaminophen 650-1000mg PO

Prior Grade 2 Infusion Reaction	24-3 hours prior to Elotuzumab Infusion	30mg PO Dexamethasone
	90-45 min prior to Elotuzumab	10mg IV Dexamethasone Diphenhydramine 50 mg IV or PO or equivalent H1 blocker Ranitidine 50mg IV or equivalent H2 blocker Acetaminophen 1000mg PO

Prior Grade 3 Infusion Reaction or recurrent Grade 2	24-12 hours prior to Elotuzumab Infusion	8mg PO Dexamethasone
	No more than 3 hours prior to Elotuzumab Infusion	14mg PO Dexamethasone
	90-45min prior to Elotuzumab	18mg IV Dexamethasone Diphenhydramine 50 mg IV or PO or equivalent H1 blocker Ranitidine 50mg IV or equivalent H2 blocker Acetaminophen 1000mg PO

5.3 **Agent Administration**

The order in which elotuzumab and lenalidomide are administered does not matter.

5.3.1 Elotuzumab

Elotuzumab will be administered intravenously at a dose of 10 mg/kg on Days 1, 8, 15 and 22 for the first 2 cycles (a cycle =28 days). During cycles 3 through 8, elotuzumab will be given on days 1 and 15. Elotuzumab will be administered intravenously at a dose of 20 mg/kg only on Day 1 for cycles 9-24. The patient should be observed for 60 minutes after the infusion is complete for cycle 1 and should be observed for 30 minutes after the infusion for subsequent cycles. All patients should have their vital signs checked before and after elotuzumab infusion or per institutional standard. If an infusion reaction occurs, reference section 6.4.2 for guidelines on additional vital monitoring.

Cycle 1 and Cycle 2 treatment may be administered +/- 3 days. For subsequent cycles +/- 7 days is allowed.

5.3.1.1 Guidelines for Elotuzumab infusion in subjects with infusion reactions

Please refer to section 6.4 of the protocol.

5.3.1.2 Dose Delay or Interruption

Please refer to section 6.4.3 of the protocol.

5.3.2 Lenalidomide

Lenalidomide will be given as a single daily oral dose of 25 mg per day on days 1-21 followed by a 7-day rest period for cycles 1-8 and 15 mg per day on days 1-21 for cycles 9-24. Cycle 1 and Cycle 2 treatment may be administered +/- 3 days. For subsequent cycles +/- 7 days is allowed. Dose modification guidelines are described in Section 6.2 (Dose Modifications/Delays).

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Administration of lenalidomide should be at approximately the same time each day. Drug may be taken with or without food. If a dose is missed and less than 12 hours has elapsed since the missed dose, the patient can take the dose for that day. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. If a dose is missed, it should be taken as soon as possible on the same day. If a dose is vomited, the dose should not be made up and the participant should continue with the regular schedule of the drug at the next dose. A drug diary will be provided to participants to record oral administration of doses.

Participants who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately. Participants experiencing adverse events may need study treatment modifications (see Section 6.2).

Lenalidomide related resources will be provided to all patients prior to receiving lenalidomide therapy as part of the Revlimid REMS program. For more information regarding program registration and drug ordering, refer to section 8.2.

5.3.2.1 Dose Delay or Interruption

Dose modification and delay guidelines are described in Section 6.2 (Dose Modifications/Delays)

5.3.3 Dexamethasone

Dexamethasone will be obtained by commercial supply in this study. This may lead to added costs for the participant or the participant's insurance company. It will be given as an oral dose. Dexamethasone should be taken at approximately the same time each day. Doses of oral dexamethasone should be taken with food and administered per the recommended guidelines in Table 3. It is recommended that dexamethasone be taken in the morning to reduce insomnia. A drug diary will be provided to participants to record oral administration of doses.

Please refer to Section 5.1 for instructions on dexamethasone dosing.

5.3.3.1 Dose Delay or Interruption

Dose modification and delay guidelines are described in Section 6.3 (Dose Modifications/Delays).

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Medications permitted at Investigator's Discretion

- Steroids, diphenhydramine, or hydroxyzine, acetaminophen/ paracetamol, H2 inhibitors (e.g., cimetidine), leukotriene inhibitors (montelukast sodium) for the management of elotuzumab infusion reactions. Additional supportive measures should be provided as indicated including oxygen inhalation, epinephrine, and bronchodilators.

- At the discretion of the treating investigator, patients will receive Pneumocystis jiroveci pneumonia (PJP) prophylaxis during treatment (Bactrim or acceptable alternative). This may be discontinued at the start of maintenance therapy, or at the investigator's discretion.

- Stem cell mobilization will be allowed at the time of best response or at the end of 8 cycles for patients who are eligible for stem cell transplant. Stem cell collection may be done sooner after discussion with overall PI. Standard mobilization treatment (with GCSF or with cyclophosphamide or plerixafor, etc) will be used based on Institutional guidelines. Patients may delay treatment for up to 3 weeks after stem cell collection is complete.

- Use of white cell growth factors [G-CSF (Filgrastim or acceptable equivalent)] is allowed for management of treatment induced neutropenia at physician discretion. Daily use of Filgrastim is not allowed, and participants may receive a maximum of 3 doses per week. Filgrastim should be given according to the ASCO guidelines. Pegfilgrastim is not to be used in replace of filgrastim.

- Patients will receive bisphosphonates per recommendations of myeloma therapy. A note should be placed about patients who are not receiving bisphosphonates for clinical reasons such as osteonecrosis of the jaw.

- Nausea/Vomiting: If nausea and/or vomiting is noted at any point in time, premedication with prochlorperazine or other antiemetics may be used before future doses. If nausea persists in spite of the use of standard antiemetics additional symptom management should be as per standard antiemetic guidelines.

- Thromboprophylaxis is required for all participants. Participants may receive

daily aspirin administration (81 or 325 mg), daily enoxaparin (40 mgs), or low molecular weight heparin (type Innohep® 4500 UI anti-Xa as needed) or equivalent to decrease the risk of thromboembolic complications. Aspirin prophylaxis will be the preferred first choice unless contraindicated. It is recommended that if the platelet count falls below 50,000/mm3, thromboprophylaxis be held to minimize the risk of bleeding and then resumed when platelet counts are equal to or above this level.

- **For patients at high risk for thromboembolic events, full anticoagulation is recommended**.

5.5 Criteria for Taking a Participant Off Protocol Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for *24 cycles* or until one of the following criteria applies:

- Disease progression
  - *Participants who have developed symptoms similar to CRAB criteria or MDE (see section 2.4), but are not attributable to active, symptomatic myeloma may remain on study after discussion with the Overall PI.*
- 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.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff. External sites should submit the form to the Research Project Manager.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Irene Ghobrial at telephone # 617-632-4198.

5.6 **Duration of Follow Up**

Participants will be followed for up to ***3 years*** after removal from protocol therapy or until progression to active symptomatic MM, whichever occurs first. Assessments will be performed every 3 to 6 months (+/- 28 days) for up to 3 years. Patients who have undergone stem cell mobilization will also be followed for 3 years after removal from protocol therapy or until progression to active symptomatic myeloma, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Participants unable to participate in follow up every 3 months may follow up every 6 months at PI discretion in accordance with standard of care follow-up frequency and COVID precautions. Physical exams and correlative blood draws that are not done due to virtual visits will not be considered violations. Local myeloma labs must be provided to the participating site for data entry purposes. Bone marrow biopsy and scans are strongly recommended yearly after EOT, but not require however, scans and bone marrow biopsy and research samples are required at time of suspected disease progression

The following is required during the Active Follow Up period (for up to 3 years):

1. Physical exams are voluntary during this period
    a. Virtual visits/telehealth visits are acceptable
2. SPEP and Immunofixation
3. Serum Free Light Chains (SFLC)
4. UPEP and Immunofixation only for those where disease is tracked by the urine
5. Serum Immunoglobulin test
6. PET/CT assessments are strongly recommended yearly and is required at the time of suspected progression
    a. The same assessment modality should be used consistently across the duration of the trial
7. Bone marrow biopsies are and strongly recommended yearly after EOT and is required at the time of suspected progression
8. Research bone marrow samples will be collected at the time of any bone marrow biopsy/aspirate procedure
9. Research blood will be collected whenever an in person visit to the site occurs. Research blood samples that are not collected at time points in the collection calendar due to COVID precautions or q6 month follow up will not be considered violations unless it is missed at the time of suspected progression.
10. Response
11. CRAB/MDE Assessment
12. Bone marrow biopsy/aspirate results and cytogenetics/FISH if ordered
13. Scan results and modality

Participants who come off active follow up when they pursue other SMM or MM directed therapy will be followed for survival indefinitely which will capture survival stats, and subsequent therapy information.

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
- Completion of 3 years of 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).

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Elotuzumab

No dose reductions for elotuzumab are allowed. If Elotuzumab is held on Day 1 of a new cycle, treatment with Lenalidomide/Dexamethasone will also be delayed. If Elotuzumab is held during any cycle on days 8, 15, or 22, the treating investigator will decide if Lenalidomide will be held using recommended guidance for retreatment below. Dexamethasone should always be given with Elotuzumab. The dose of dexamethasone may be modified per guidance below. Treatment may be delayed for a maximum of 21 days. If a patient must discontinue treatment with lenalidomide, they may continue to receive elotuzumab on study after discussion with the overall principal investigator.

If a patient must discontinue elotuzumab for unacceptable toxicity, they may continue to receive lenalidomide and dexamethasone on study after discussion and approval of the overall principal investigator.

6.2 Lenalidomide

Patients may hold treatment of lenalidomide for up to 21 if the toxicity is considered either possibly, probably or definitely related to the drug. Patients may hold lenalidomide for greater than 21 days only after discussion and subsequent approval of the overall principal investigator.

Hematologic Toxicities: For adverse hematologic events that are considered possibly, probably or definitely related to Lenalidomide, the following criteria for retreatment and dose modification should be followed. Treatment may be held for a maximum of 21 days. Refer to Table 4 for dose reduction levels for Lenalidomide.

Non Hematologic Toxicity: For adverse non hematologic events that are considered to be possibly, probably or definitely related to Lenalidomide, the following criteria for retreatment and dose modification should be followed. The treating investigator should determine the clinical significance of laboratory values or radiographic findings and attribution to study medications before a treatment decision is made. Treatment may be held for a maximum of 21 days. Refer to Table 4 for dose reduction levels for Lenalidomide.

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Hematologic Toxicities

CTCAE 4.0 Category	CTCAE Grade	Lenalidomide Dose Modification
Absolute Neutrophil Count (ANC)[1]	**Grade 1 or Grade 2**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy
	Grade 3	Hold dose Administer Filgrastim Resume at same dose when ANC is ≥ 1000 if neutropenia is the only hematologic toxicity If other hematologic toxicity ≥Grade 2 is present, reduce dose one level when ANC≥1000
	Grade 4	Hold dose Administer Filgrastim Resume therapy at one dose level lower when ANC is ≥ 1000
Neutropenia with Fever ANC <1000 and temperature ≥38.5° C or 101°F	**Grade 3 or Grade 4**	Hold dose Administer Filgrastim Reduce dose one level when ANC≥1000
Thrombocytopenia Aspirin prophylaxis should be held if platelets are ≤50,000	**Grade 1 or Grade 2**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy
	Grade 3 or Grade 4	Provide platelet transfusion support Redraw platelets If redrawn platelet value ≥ 50,000 -> Do NOT OMIT and DO NOT REDUCE therapy If redrawn platelet value <50,000 continue to transfuse at the discretion of the investigator and hold therapy until platelets are ≥ 50,000 on Day 1 or ≥ 30,000 intracycle

		Resume therapy at one dose level lower when the patient's platelets are ≥ 50,000 on Day 1 or ≥ 30,000 intracycle
Anemia	**Grade 1** **Grade 2** **Grade 3**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy Transfuse at the discretion of treating investigator
	Grade 4	Hold treatment Transfuse Resume treatment when hemoglobin ≥ 8.0 g/dL DO NOT REDUCE therapy

[1] ANC can be calculated two ways: From the percentage of neutrophils: White Blood Count (WBC) x total neutrophils (polys% + bands%) x 10. From the absolute number of cells: (Absolute polys + Absolute bands) x 10.

Non Hematologic Toxicities

CTCAE 4.0 Category	CTCAE Grade	Lenalidomide Dose Modification
Infection or Viral Illness with ANC[1] ≥1000 Including herpes zoster reactivation	**N/A**	Day 1 of Cycle: Delay cycle until infection/viral illness has resolved. Resume treatment at the same dose level. Do not dose reduce. Intracycle: Hold lenalidomide for a maximum of 21 days to allow for recovery. Resume treatment at same dose level. If patient has delay of greater than 21 days, the patient must come off-study
Infection or Viral Illness with ANC[1] < 1000	**N/A**	Day 1 of Cycle: Delay cycle until infection/viral illness has resolved. Administer filgrastim or equivalent as indicated. Reduce one dose level when infection/virus has resolved, and ANC ≥1000 Intracycle: Hold lenalidomide for a maximum of 21 days. Reduce one dose level when infection/virus has resolved and ANC ≥ 500 If patient has a delay of less than or equal to 21 days, dose reduce to next dose level. If patient has delay of greater than 21 days, the patient must come off-study
Allergic reaction or hypersensitivity to	**Grade 1**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy

Lenalidomide Including Rash related to Lenalidomide	**Grade 2**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy
	Grade 3 **or** **Grade 4**	Hold lenalidomide Follow at least weekly. If toxicity resolves to ≤ grade 2, restart at next lower dose level

Renal/Metabolic For all grades, provide hydration and other supportive care as needed at the discretion of the treating investigator	**Grade 1**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy
	Grade 2	Hold Lenalidomide until < grade 2 and resume treatment at the same dose level If toxicity recurs, dose reduce one dose level at the treating investigator's discretion
	Grade 3 **or** **Grade 4**	Hold Lenalidomide until < grade 2 and resume treatment with one dose level reduction If the toxicity remains ≥ grade 3, omit dose and restart at subsequent scheduled visit with one dose level reduction If treatment-related toxicity occurs on day one of the cycle, the cycle will be delayed.
Diarrhea, Constipation, Nausea, or Vomiting	**Grade 1**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy
	Grade 2	Treat at the discretion of the investigator Provide aggressive supportive care DO NOT REDUCE therapy
	Grade 3	Hold Lenalidomide until toxicity resolves to < grade 2 If the patient has received maximum supportive care, resume therapy with one dose level reduction
	Grade 4	Hold Lenalidomide until toxicity resolves to < grade 2 Resume therapy with one dose level reduction

All other related toxicities not listed previously in this table	**Grade 1**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy
	Grade 2	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy unless considered to be a clinically significant finding Provide supportive care as needed
	Grade 3	Hold Lenalidomide until toxicity resolves to < grade 2 Resume therapy with one dose level reduction at the discretion of the treating investigator
	Grade 4	Hold Lenalidomide until toxicity resolves to < grade 2 Resume therapy with one dose level reduction If treatment-related toxicity occurs on day one of the cycle, the cycle will be delayed. If patient has a delay of less than or equal to 21 days, dose reduce to next dose level. If patient has delay of greater than 21 days, the patient must come off-study

[1] ANC can be calculated two ways: From the percentage of neutrophils: White Blood Count (WBC) x total neutrophils (polys% + bands%) x 10. From the absolute number of cells: (Absolute polys + Absolute bands) x 10

Table 4 Lenalidomide Dose Reduction

Dose Level	**Lenalidomide Dose**
Starting Dose Level	25 mg
First Dose Reduction	20 mg
Second Dose Reduction	15 mg
Third Dose Reduction	10 mg
Fourth Dose Reduction	5 mg

6.3 **Dexamethasone**

Dexamethasone Dose Modifications

Premedication with dexamethasone is required prior to all elotuzumab infusions. If there are clinically significant, intolerable ≥Grade 3 adverse events attributed to dexamethasone (given as a premedication) treatment may be delayed until recovery to ≤ Grade 2 at the discretion of treating investigator. For adverse events that are considered to be possibly, probably or definitely related to dexamethasone, the following criteria for retreatment and dose modification should be followed. The treating investigator should determine the clinical significance and attribution of the toxicity to dexamethasone. If toxicity is unlikely or not related to dexamethasone, do not omit or reduce therapy. Patients may continue on study if oral dexamethasone has been permanently discontinued

Patients who have not experienced an infusion reaction related to elotuzmab and have experienced an adverse event attributable to dexamethasone may have their premedication of dexamethasone decreased after completion of cycle 1 at the discretion of the treating investigator and after discussion with the overall PI.

CTCAE 4.0 Category	**CTCAE Grade**	**Dexamethasone Dose Modification**
Hyperglycemia Treat with oral medication or insulin at discretion of treating investigator	**Grade 1**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy
	Grade 2	Hold dexamethasone until < Grade 2 and resume at same dose level at the discretion of the treating investigator
	Grade 3	Hold dexamethasone until < Grade 2 Resume therapy with one dose level reduction at the discretion of the treating investigator
	Grade 4	Hold dexamethasone until < Grade 2 Resume therapy with one dose level reduction
Symptomatic pancreatitis	**Any Grade**	Discontinue dexamethasone permanently
OTHER	**Grade 1 or 2**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy
	Grade 3	Hold dexamethasone until ≤ Grade 2 Resume therapy with one dose level reduction
	Grade 4	Hold dexamethasone ≤ Grade 2 Resume therapy with one dose level reduction

Table 5 Dexamethasone dose reduction

Total Dexamethasone Dose Administration for Patients with none or Prior Grade 1 Infusion Reaction

Dose Levels	Week with Elotuzumab		Week Without Elotuzumab*	
	PO	IV	PO	IV
Starting Dose Level	32	8	40	0
First Dose Reduction	28	8	20	0
Second Dose Reduction	28	8	10	0

* During Maintenance, patients only receive dexamethasone on Day 1

Total Dexamethasone Dose Administration for Patients with Prior Grade 2 Infusion Reaction

Dose Levels	Week with Elotuzumab		Week Without Elotuzumab*	
	PO	IV	PO	IV
Starting Dose Level	30	10	40	0
First Dose Reduction	28	10	20	0
Second Dose Reduction	28	10	10	0

* During Maintenance, patients only receive dexamethasone on Day 1

Total Dexamethasone Dose Administration for Patients Prior Grade 3 or recurrent Grade 2 Infusion Reaction

Dose Levels	Week with Elotuzumab		Week Without Elotuzumab*	
	PO	IV	PO	IV
Starting Dose Level	22	18	40	0
First Dose Reduction	16	18	20	0
Second Dose Reduction	16	18	10	0

* During Maintenance, patients only receive dexamethasone on Day 1

** If patient is intolerant of dexamethasone, after discussion with overall PI, oral dexamethasone may be omitted at any dose level.

6.4 Guidelines for Elotuzumab Infusion in Subjects with Infusion Reactions

6.4.1 Grade 1 Infusion Reaction

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

6.4.2 Grade ≥2 Infusion Reaction

Infusion reactions during the elotuzumab infusion: For a Grade ≥ 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: antiemetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

Subjects with a Grade 3 infusion reaction may be discontinued from study drug at the discretion of the investigator, but must be discontinued if the Grade 3 infusion reaction recurs. Subjects with any Grade 4 infusion reaction are not eligible to receive additional elotuzumab.

If a patient's elotuzumab regimen is discontinued before the completion of cycle 2, he or she must come off protocol therapy. If elotuzumab is discontinued after completion of cycle 2, he or she can remain on protocol therapy.

Once the elotuzumab infusion-related reaction has resolved to ≤ Grade 1, the infusion can be restarted at 0.5 mL/minute. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion (0.5 mL/minute every 30 minutes) to a maximum of 2 mL/minute or the rate at which the infusion reaction occurred, whichever is lower. Subjects who experience an infusion reaction require vital signs to be monitored approximately every 30 minutes for up to 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 previously.

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

Elotuzumab infusions on subsequent weeks after a prior Grade ≥2 infusion reaction: Subjects with prior Grade 2 or higher infusion reactions should have future infusions started at 0.5 mL/min and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes). If no Grade ≥ 2 infusion reaction recurs, the escalation regimen may be resumed and the next infusion may be initiated as planned per the regimen.

If a patient experiences an infusion reaction of less than or equal to Grade 2, and the infusion reaction does not recur, the patient can resume elotuzumab administration at the rate at which the reaction occurred at the start of the next cycle at the investigator's discretion

6.4.3 Dose Delay or Interruption

If a patient's elotuzumab administration is delayed on day 1 of a cycle, both lenalidomide and dexamethasone will also be delayed until the elotuzumab is resumed, which would then become

the new day 1 of that cycle.

If a patient's elotuzumab is held in the middle of a cycle, lenalidomide dosing will continue as scheduled. If the patient's elotuzumab is delayed during the cycle and is resumed within the designated window, (+/-3 days Cycles 1 and 2; +/-7 days Cycles 3 and beyond) the patient may receive that scheduled dose. If the elotuzumab is not resumed within the given window (+/-3 days Cycles 1 and 2; +/-7 days Cycles 3 and beyond), the patient is to omit that dose, and resume dosing at the next dosing time point. Dexamethasone should be held and resumed when Elotuzumab is held and subsequently resumed.

Patients may delay treatment for up to 3 weeks for elective surgeries and other non toxicity related events.

Table 6: Dose Delay Instructions

	To be resumed within window?	**Lenalidomide**	**Dexamethasone**	**Elotuzumab**
Elotuzumab delayed on Day 1 of Cycle	N/A	To be delayed until Elotuzumab is resumed	To be delayed until Elotuzumab is resumed	Resume dosing= new Day 1 of Cycle
Elotuzumab held on Day 8,15,or 22 of Cycle	Yes	Dosing to continue as scheduled	To be delayed until Elotuzumab is resumed	Resume dose any day within window; dose time point not skipped
Elotuzumab held on Day 8,15, or 22 of Cycle	No	Dosing to continue as scheduled	To be delayed until Elotuzumab is resumed	Resume dosing at next dosing time point (skip dose)

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events List(s)

7.1.1.1 Adverse Event List of 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.

7.1.1.2 Adverse Event List for Lenalidomide

Events that have occurred in >10% of individuals treated with lenalidomide include neutropenia, anemia, thrombocytopenia, fatigue, rash, diarrhea, constipation, nausea, loss of appetite, itching, dry skin, muscle cramps, lack or loss of strength, dizziness, insomnia, swelling of the extremities, headache, back and joint pain, fever, cough, upper respiratory infection, and dyspnea.

Events that have occurred in >1% of individuals treated with lenalidomide include risk of DVT, PE, and blood clots that could lead to stroke, heart attack, or organ failure, febrile neutropenia, atrial fibrillation, pneumonia or lung infections, sepsis, dehydration and renal failure.

Events that have occurred in <1% of individuals treated with lenalidomide include rare treatment-emergent adverse events of angioedema, serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) or an allergic skin reaction similar to that seen with thalidomide, tumor lysis syndrome (TLS), tumor flare reaction (TFR), and rhabdomyolysis. In addition, lenalidomide has been shown to increase the level of digoxin in the blood in some patients. Patients will be instructed to inform their doctor if taking digoxin.

There may be an increased risk of second cancers in patients who are on lenalidomide maintenance therapy after a bone marrow transplant.

7.1.1.3 Adverse events list of Dexamethasone

Events that have occurred in 10-15% of individuals treated with dexamethasone include increased appetite, weight gain, sleep disturbance, hypertension, fluid retention, ankle swelling, bruising, infection, mood changes, slow wound healing, depression, and hyperglycemia, which may lead to fatigue, weight loss, excessive thirst and frequent urination. Events that have occurred in 1-9% of individuals treated with dexamethasone include loss of appetite, muscle twitching, increased thirst, frequent urination, increased perspiration, diarrhea, nausea, headache, bone thinning, spinal fracture or fracture of bones, tachycardia, fungal infections. Events that have occurred in <1% of individuals treated with dexamethasone include blurred vision, personality changes, stomach ulcers with bleeding that may cause hematemesis, blood in the stool and abdominal pain. Other, less frequent, events may include bowel perforation, irritation and bleeding of the esophagus, heart failure, allergic reaction that may lead to facial redness, shortness of breath, abdominal cramps and 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, facial puffiness, leading to the appearance of a

"moon face" hormonal disturbances, and hiccups.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 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 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **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, all grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.4 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 Overall PI within the timeframes detailed in the table below.

DF/HCC Reportable AEs					
Attribution	**Gr. 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# 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 1 business day of learning of the event.					

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

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 will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

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. The investigator must immediately notify the BMS, Celgene (or designee) Medical Monitor of this event and complete and forward an SAE Form to BMS and Celgene (or designee) within 24 hours and in accordance with SAE reporting procedures described in this section.

Pregnancy

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Overall PI. Information on this pregnancy will be collected on the BMS Pregnancy Surveillance Form. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form. Please contact the Research Project Manager if you do not have this form in your regulatory files.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28

days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the 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.

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 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.

Male Subjects
If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Celgene Drug Safety Contact Information:

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

Overdose

Include any product-specific definition of overdose in addition to the following mandatory statement as the last sentence.
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.

Overdose of Lenalidomide

Overdose, as defined for this protocol, refers to Revlimid dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of Revlimid assigned to a given patient, regardless of any associated adverse events or sequelae.

- PO any amount over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

7.4.1 Protocol-Specific Expedited Adverse Event Reporting Exclusions

There are no protocol specific exclusions.

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, 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 Bristol-Myers Squibb (BMS)

The Overall PI, as study sponsor, will be responsible for all communications with the BMS. With the exception of any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA. All SAEs and SUSARs should simultaneously be faxed or e-mailed to BMS by each participating site at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

The written report must be completed and supplied to BMS by facsimile or e-mail within 3 business days.. The report should also include the BMS trial number, which is CA204-119.

7.7 Expedited Reporting to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of

being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-MM-PI-004473) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

7.8 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.

7.9 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 Elotuzumab and lenalidomide administered in this study can be found in Section 7.

8.1 Elotuzumab

8.1.1 Description

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

8.1.2 Form

Elotuzumab for injection has been developed to be used as an intravenous (IV) infusion for the 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.

Table 7

Product	Potency	Primary	Secondary	Appearance	Storage

Description and Dosage Form		Packaging (Volume)/ Label Type	Packaging (Qty) /Label Type		Conditions (per label)
Elotuzumab Powder for Solution for Infusion	400mg/vial	20 ml vial/ open Label	10 vials per kit/open Label	Sterile, white to off-white, preservative-free, lyophilized cake	Store at 2°C - 8°C

8.1.3 Storage and Stability

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

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, and then further diluted in 0.9% sodium chloride normal saline, USP, as per the instructions in Appendix B. After the dose is diluted in normal saline, it 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 by the pharmacist in study drug accountability records. The dose of elotuzumab to be administered to a subject will be calculated by multiplying the subject's weight (kg) by 10 mg/kg. The subject's predose weight on Day 1 of each cycle or predose weight at each visit, whichever is institutional policy, will be used to calculate the dose for each cycle. Each dose should be infused as per instructions in Appendix B.

8.1.4 Handling

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, and then further diluted in 0.9% sodium chloride normal saline, USP, as per the instructions in Appendix B.

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

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

After the dose is diluted in normal saline, it 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 by the pharmacist in study drug accountability records.

8.1.7 Administration

Elotuzumab will be given cycle 1 & 2 at 10 mg/kg IV once a week (days, 1, 8, 15, and 22). Elotuzumab will be given cycle 3 to 8 at 10mg/kg IV days 1 and 15 every cycle. Maintenance elotuzumab will be given at 20 mg/kg IV day 1 every cycle up to cycle 24 (total of 2 years).

8.1.8 Ordering

The investigator or designee will order drug from Bristol-Myers Squibb, according to the ordering instructions provided by company. A study specific order form will be provided by the lead site.

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 investigator'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 **Lenalidomide**

8.2.1 Description

Lenalidomide (REVLIMID®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H- isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

3-(4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3.

8.2.2 Form

Lenalidomide is off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

Lenalidomide is available for this study as 5 and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

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. Lenalidomide 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 lenalidomide 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

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through Celgene's Revlimid Risk Evaluation and Mitigation Strategy™ (REMS) (formerly known as RevAssist® Program, Research). Each patient's individual drug supply will be delivered to the site by the drug courier Biologics and be distributed to the patient through the research side of the pharmacy of that site.

8.2.6 Preparation

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

8.2.7 Administration

Lenalidomide will be given daily at 25 mg days 1-21 on a 28 day cycle, cycles 1-8. Maintenance therapy can be given until cycle 24 (total of 2 years). During maintenance, lenalidomide will be given 15 mg daily days 1-21 every cycle.

At all times when dispensing lenalidomide protocol therapy, study site personnel will review the instructions, printed on the packaging, with participants.

8.2.8 Ordering

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide 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 Revlimid REMS® program. Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle**.

Lenalidomide will be shipped directly to the clinic site. Bottles will contain a sufficient number of capsules for one cycle of dosing**.** A study specific order form will be provided by the lead site.

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

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator'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. The unused study drugs should be destroyed per institutional policies after the drug returns have been reconciled by the monitor, or when the lead site instructs the site to do so.

If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

8.3 **Dexamethasone**

8.3.1 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.

8.3.2 Form

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 2 or 4 mg tablets (commercially) for oral administration. Each tablet contains dexamethasone as the active ingredient, and the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch. The tablet shell may contain the following: D&C Yellow 10, FD&C Yellow 6, and/or FD&C Blue 1.

8.3.3 Storage and Stability

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Dexamethasone should be stored at controlled room temperature, 68-77◦F (20-25◦C) and not frozen, and according to label requirements.

8.3.4 Handling

Dexamethasone should be handled by trained pharmacy staff. The use of gloves and other appropriate protective clothing is recommended as necessary.

8.3.5 Availability

Dexamethasone supply will be obtained through commercial supply.

8.3.6 Preparation

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

8.3.7 Administration

, Participants will receive dexamethasone Days 1, 8 15 and 22 during cycles 1-2 and then days 1, 8, 15 on cycles 3-8 and on day 1 of cycles 9-24 of maintenance .

8.3.8 Ordering

The investigator or designee will order drug supply from commercial supply.

8.3.9 Accountability

As drug is from commercial supply, sites should keep records per their institutional policies.

8.3.10 Destruction and Return

At the end of the study, unused supplies of dexamethasone should be destroyed and documented according to institutional policies.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

This trial will provide samples high-risk SMM patients treated with elotuzumab and lenalidomide to comprehensively characterize the MM genome and immune cells function and define molecular events driving development and progression of MM.

We will attempt to obtain samples on all patients at the following time points: before therapy, at the end of cycle 8, at the time of response determination (CR) , at disease relapse, and at several more time points over the course of the study. It is anticipated that approximately 90% of samples collected will be adequate for sequencing studies proposed.

The tumor cells will be collected as described below. From these samples, high quality DNA (for tumor cells) and RNA (for tumor cells and immune cells) for both exome sequencing and RNA sequencing will be obtained. Germline DNA will be also obtained from a buccal swab from all patients at any time point of the study.

Peripheral blood and bone marrow derived mononuclear cells will undergo immunologic assessments to assess the impact of therapy on general measures of cellular immunity, MM reactive T cells, and antigen specific immunity. The percentage of circulating and bone marrow derived regulatory T cells, NK cells and MDSCs will be determined. The percent of PD-1 and other checkpoint regulators on immune cells will also be measured. Levels of naïve, effector and central memory cells will be quantified. T cell proliferative response to tetanus toxoid and PHA mitogen will be determined. NK cell mediated cytotoxicity will be measured.

We will also determine the level of SLAMF7 on these cells.

In addition, we will examine the level of soluble SLAMF7 pre-treatment and monthly on Day 1 of each cycle.

Peripheral blood and bone marrow samples will be collected at the screening time and for analysis in order to confirm response as well as at C9D1. The collection kits and shipping supplies will be provided to the sites by Sequenta. These samples will be packaged whole, and shipped to Sequenta, Inc. in South San Francisco, CA same day priority overnight.. Using Sequenta's LymphoSIGHT platform, rearranged immunoreceptor loci from genomic DNA will be extracted, amplified, and sequenced using V and J segment primers for each immunoreceptor gene. Tumor-specific clonotypes will be identified for each patient based on their high prevalence in peripheral blood. Sequences will be analyzed using standardized algorithms for clonotype determination. Sequenta MRD levels will be quantified using spiked-in reference sequences.

9.1 **Bone Marrow Aspirate Samples**

Collection of bone marrow aspirate specimens for exploratory analysis will be requested for this trial. Collections that are requested will be obtained at screening, C9D1, confirmation of CR and at end of study treatment. At any time a bone marrow aspirate procedure is performed, an additional sample for exploratory analysis is requested. This will not require extra access for participants. Specimens will be shipped (via traceable carrier) to and subsequently processed, analyzed, and stored at Dana-Farber Cancer Institute.

Specimens Requested: 2 Purple Top Tubes (K2EDTA), 10mL each. Specimens must be collected on Mondays to Thursdays for same-day shipment.

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

Shipping Information for Bone Marrow Aspirate Specimens: Label all specimens with the following: Subject Initials, Subject study number (will include protocol number), Visit at which sample was drawn (screening, response or relapse/progression), Date sample drawn (mm/dd/yyyy), Time sample drawn (24 hour clock)

9.1.1 Shipping Instructions:

Shipments must be sent on the day of collection and cannot be batched.

1. An inventory sheet including a complete list of samples shipped (patient number, timepoint, study #) must accompany each shipment. Please sign and date the requisition form.

2. An electronic copy (Word or Excel) of the sample list must also be sent via email. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.

3. Please email the lead site contact to notify of an incoming shipment.

4. Please ship **ONLY** Monday to Thursday as shipments cannot be received on weekends and/or on holidays.

5. Once drawn, samples may be shipped **via overnight air** to:

   Dana Farber Cancer Institute
   Ghobrial Lab
   360 Longwood Avenue LC8116
   Boston, MA 02215
   Email: GhobrialLab@dfci.harvard.edu

   Please retain a copy for site record maintenance. **Please see Appendix C and D for Collection Schedule and Requisition Form**

9.2 Peripheral Blood Samples

Collection of peripheral blood specimens (including serum and plasma) for exploratory analysis are requested for this trial. Purple top tube collections should be obtained at the same timepoints as bone marrow samples for correlative studies (see Section 10 for list of required timepoints, and Appendix C for specific instructions). These collections will be taken at the time of routine blood collection timepoints required for this study. Specimens will be processed on site according to instructions below and shipped (via traceable carrier) to Dana-Farber Cancer Institute. Once the shipment is received, samples will be subsequently processed, analyzed, and stored at Dana-Farber.

9.2.1 Specimens Required: 2 x 10ml Purple Top Tubes (K2EDTA), and 1x 6ml Red Top (no additive) tube, must be collected Mondays to Thursdays for same-day shipment.

9.2.2 Shipping Information: Label all specimens with the following:

- Subject Initials
- Subject study number (will include protocol number)
- Visit at which sample was drawn (screening, response or relapse/progression)
- Date sample drawn (mm/dd/yyyy)
- Time sample drawn (24 hour clock)

9.2.3 Processing Information**:** Once collected, the vacutainers will be refrigerated and stored according to instructions below. There is no required processing for purple top tubes at each participating site prior to shipment.

9.2.4 Shipping Instructions: Shipments must be sent on the day of collection and cannot be batched.

Processing Information:

Invert each tube 5 times at blood collection to ensure adequate mixing of anticoagulant with blood immediately after the blood collection. Package tubes at room temperature and wrap in a liberal amount of paper towel around the tubes to ensure adequate insulation of the specimen(s) and absorption in the event of a breakage. Place wrapped specimen in a biohazard labeled Ziploc

bag with a fridge pack and zip close. Wrap bubble wrap around the bag and place in a cardboard box. If space remains in the box, stuff with extra paper towel to reduce shifting of samples. Complete the shipping requisition form using the address listed below. Prepare the package for shipping, applying packing tape as needed. Ship the package using FedEx or UPS next day or overnight delivery the same day the sample was collected. Please only ship Monday-Thursday, as the lab is only able to accept Saturday shipments with 1 week advance notice. With each shipment, please include the following:

1. An inventory sheet including a complete list of samples shipped (patient number, timepoint, study #) must accompany each shipment. Please sign and date the form, and retain a copy for site record maintenance. **See Appendix D for Sample Requisition Form**

2. An electronic copy (Word or Excel) of the sample list must also be sent via email and include the tracking number of the package. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.

3. Please email the Dana-Farber/lead site contact to notify of an incoming shipment.

4. Please ship Monday to Thursday as shipments cannot be received on weekends and/or on holidays.

5. Once drawn, samples may be shipped **via overnight air to:**

   Dana Farber Cancer Institute
   Ghobrial Lab
   360 Longwood Avenue LC8116
   Boston, MA 02215

   Email: GhobrialLab@dfci.harvard.edu

For Sequenta samples, use the packing supplies provided in each individual kit and follow the directions below:

1. Label each tube with date of collection, patient's study specific number, initials, and date of birth

2. Store collected tubes at room temperature until same day shipment.

3. On the ClonoSEQtest requisition form, fill out requisition with patient first and last name, date of birth, and gender. Ordering physician should be listed as Irene Ghobrial, MD. Please ensure that the sample tubes are labeled, and reference patient specific study number, the treating site, and the treating physician name at the top of the requisition form.

4. Under ICD-10, Other: Multiple Myeloma C90.00 should be entered

5. Under specimen information, enter collection date under fresh specimens, and mark which samples have been provide (blood and bone marrow)

6. For baseline samples, ClonoSIGHT ID Test should be checked. For confirmation of response time point, ClonoSIGHT MRD Test should be checked.

7. Under billing, please provide insurance information for the patient

8. Complete pathology, physician signature, and billing information sections

9. Please make a copy of the requisition to retain for your records along with the Fed-Ex tracking number in the event that the package is lost.

10. Follow the sample packing instructions included in the kit, and send out same day. Shipping on Friday is ok for Saturday processing for these samples.

11. An electronic notification must be sent via email and include the tracking number of the package, and all relevant sample information and patient identifiers to the study team The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.

    a) Please email the lead site contact to notify of an incoming shipment.

10. STUDY CALENDAR

Screening evaluations are to be conducted within 28 days prior to initiation of registration. Protocol therapy should start as soon after registration as feasible. Baseline assessments are to be conducted on C1D1 of initial therapy and should be considered separate from screening evaluations. Evaluations need not be repeated for C1D1 if screening evaluations are performed within 7 days of registration. Scans and bone marrow assessments do not need to be repeated if performed within 6 weeks of registration. All assessments must be performed prior to administration of any study medication.. See below for detailed scheduled of assessments. Study medications will be administered according to the schedule and guidelines outlined in Section 5.

	Pre-registration		**Cycles 1-24 (28 days)** [3]				**Follow Up**[11]
Tests and procedures	**≤ 28 days prior to registration**	**≤ 21 days prior to registration**	**Day 1 of all cycles**[1]	**Days 8, 15 and 22 of cycles 1 & 2** **Days 1 &15 from cycle 3-8**	**Cycle 9 Day 1/ Or to confirm CR**[9]	**End of Tx**	**Every 3 or 6 Months (+/- 28 days)**
History and exam, height, weight. Performance Status	X		X			X	(X)
Toxicity Notation			X			X	
Hematology group (WBC w/ diff, PLT, Hgb, ANC)		X	X	X		X	X
Chemistry[4]		X	X	X		X	X
Direct & total bilirubin[2]		X	X			X	
Free light chain assay		X	X			X	X
Serum and Urine Immunofixation (SPEP and UPEP) with quantitative immunoglobulins[10]		X	X			X	X
β2M, CRP, LDH		X				X	
Metastatic Bone Survey/ Spine MRI or PET/CT[12]	X					X	(X)
EKG		X				X	
Serum pregnancy test		X					
Unilateral bone marrow aspirate and biopsy[5]	X				X	X	(X)
Research bone marrow aspirate[6]	X[5]				X[6]	X[6]	(X)
Research Blood[7]	X[8]		X		X	X	(X)

1- Cycle 1, Day 1 laboratory values need to meet eligibility criteria
2- Direct bilirubin to be obtained if total bilirubin is abnormal.
3- Scheduling allows for +/- 3 days cycles 1-2 and +/- 7 days for cycle 3 and beyond.
4- Chemistry includes sodium, potassium, chloride, bicarbonate, bun, creatinine, calcium, glucose, albumin, ALT (SGPT), total protein, AST (SGOT), total bilirubin, magnesium, and phosphorus.
5- These procedures should also be done at any time during the course of the study to confirm CR.
6- Research bone marrow aspirate and biopsy at the same time of clinically indicated bone marrow biopsy and to confirm response.
7- Peripheral blood samples for correlative studies including serum SLAMF7 levels.
8- Oragene kit for germline DNA will be acquired once at any time point from patients enrolled on this study.
9-If C9D1 or confirmation of response BM biopsy was performed within 3 weeks of subsequent time point listed; do not need to repeat BM biopsy.

10- Patients who are not followed for disease response in their urine per IMWG criteria need only bring urine every third cycle and at end of treatment after baseline
11- Follow up will occur approximately every 3 to 6 months (+/- 28days) for up to 3 years after discontinuation of therapy (EOT). Participants unable to participate in follow up every 3 months may follow up every 6 months at PI discretion in accordance with standard of care follow-up frequency and COVID precautions. Physical exams and correlative blood draws that are not done due to virtual visits will not be considered violations. Local myeloma labs must be provided to the participating site for data entry purposes. Bone marrow biopsy and scans are strongly recommended yearly after EOT but are required when there is suspicion of clinical progression. These assessments can be waived due to extenuating circumstances or for insurance coverage reasons. Scans and bone marrow biopsy and research samples are required at time of suspected disease progression if one is performed as part of standard of care procedures.
12- A CD of scans at screening and end of treatment is requested to be sent to the lead site for central review. Screening scans should be sent with the eligibility packet to the lead site

(X)- Indicates this assessment may not be required
Note: Research blood and bone marrow studies are voluntary and do not exclude patients from participating

11. MEASUREMENT OF EFFECT

11.1 Development of symptomatic disease

In this study, the final endpoint is development of symptomatic MM that requires therapy. This is defined as one of the following criteria (CRAB* and Myeloma defining events< MDE):

- Increased calcium levels (corrected serum calcium >0.25 mmol/dL above the upper limit of normal or >.275 mmol/dL);
- Renal insufficiency (attributable to myeloma);
- Anemia (Hgb 2g/dL below the lower limit of normal or <10g/dL);
- Bone lesions (lytic lesions or generalized osteoporosis with compression fractures)
- Or any MYELOMA DEFINING EVENTS (MDE) as follows:
    - Clonal bone marrow plasma cell percentage*> 60%[2]
    - An abnormal FLC-ratio ≥100 (involved kappa) or ≤0.01 (involved lambda)[52]
    - 2 or more focal lesions on MRI or PET-CT studies[53,54]

* Participants with CRAB criteria that are attributable to conditions other than the disease under study may be eligible

For measurement of response:

In this study, patients must have measurable disease. The disease response will be assessed using criteria based on the International Working Group Uniform Response Criteria in Section 11.2.4. If the only measurable parameter is serum immunoglobulins free light chain (FLC), the participant will be followed by FreeLite™ Disease Response Criteria provided in Section 11.2.5.

Disease response by the Modified EBMT Response Criteria in Section 11.2.6.2 will also be collected on participants as a secondary measure.

The same method of assessment and technique should be used for disease measurement at baseline and during follow-up. Disease response should be confirmed by two consecutive

assessments.

11.2 Antitumor Effect

11.2.1 Disease Parameters

Measurable disease: Measurable disease is disease that can be measured either by serum or 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 g/dl
- Urine M-protein $\geq$ 200 mg/24 h
- Serum FLC assay: Involved FLC level $\geq$ 10 mg/dl ($\geq$ 100 mg/l) provided serum FLC ratio is abnormal.

If a patient has measurable disease, but not by IMWG standards listed above, the patient may be eligible after discussion with the Overall Principal Investigator.

11.2.2 Methods for Evaluation of Measurable Disease

All baseline evaluations should be performed on Cycle 1, Day 1 of initial therapy. Response will be assessed by M-protein quantification, protein electrophoresis and immunofixation from serum and a 24-hour urine collection. A serum sample for FreeLite™ testing will be obtained. In addition, bone marrow aspiration and biopsy, as well as skeletal survey will be performed to determine overall response or confirm response.

The same method of assessment and technique should be used for disease measurement at baseline and during follow-up.

11.2.3 Response Criteria

A confirmation measurement for disease response assessments is required in this protocol.

11.2.4 International Myeloma Working Group Response Criteria

Response criteria for all categories and subcategories of response except CR are applicable

only to patients who have 'measurable' disease, as defined in Section 11.2 All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

Stringent CR: CR as defined below plus normal free light chain ratio and absence of clonal cells in bone marrow* by immunohistochemistry or immunofluorescence.**

*Confirmation with repeat bone marrow biopsy is not needed.

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

CR: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow.
*Confirmation with repeat bone marrow biopsy is not needed.

VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 hours.

PR: ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by > 90% or to < 200mg per 24 hours. If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (definition of measurable disease in Section 10.2.3). If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 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.

SD: Not meeting criteria for CR, VGPR, PR or progressive disease. This is not recommended as an indicator of response; stability of disease is best described by providing the time to progression estimates.

PD: > 25% increase of serum M-protein (which must also be an absolute increase of ≥ 0.5 g/dL) and/or urine M-protein (which must also be an absolute increase of ≥ 200 mg/24hr). If serum and urine M-protein are unmeasurable, there must be an absolute increase of ≥ 10 mg/dL between involved and uninvolved FLC levels. PD is also measured by an absolute increase in bone marrow plasma cells ≥ 10%. In addition to the above listed criteria, progression may also be measured by a definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas or development of hypercalcemia (corrected serum calcium ≥ 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.

11.2.5 FreeLite™ Disease Response Criteria

Complete Response: For those patients being followed by serum free light chain (and NO measurable serum or urine M-spike), which were immunofixation negative at enrollment, normalization of serum free light chain ratio.

- Normalization is defined as the serum free light chain ratio being within the normal range. If the serum free light chain ratio is not within the normal range, but the individual kappa and lambda light chain values are within normal range, this may be considered CR.

Partial Response: If only measurable parameter is serum immunoglobulins free light chain (FLC), EITHER of the following changes qualify as partial response:

- A 50% decrease in the difference between involved and uninvolved FLC levels; OR

- A 50% decrease in the level of involved FLC AND a 50% decrease (or normalization) in the ratio of involved/uninvolved FLC

Progressive Disease: If only measurable parameter is serum immunoglobulins free light (FLC), either of the following qualify as progression:

- 50% increase in the difference between involved and uninvolved FLC levels from the lowest response level, which must also be an absolute increase of at least 10 mg/dL; OR

- 50% increase in the level of involved FLC AND a 50% increase in the ratio of involved/uninvolved FLC from the lowest response level.

11.2.6 Criteria for Molecular CR and Minimal Residual Disease (MRD) measurement

We will measure MRD in patients who achieve CR to determine the number of patients who are MRD negative vs MRD positive.

11.2.6.1 MRD by LymphoSIGHT

MRD will be carried out according to the LymphoSIGHT™ method (Sequenta, Inc., San Francisco, CA)[55]. Prior studies have compared this technique to the traditional MRD immunofluorescence technique, as previously reported [60] and showed that MRD by LymphoSight is a sensitive method that can be used in future clinical practice.

For MM diagnostic samples, genomic DNA will be amplified using locus-specific primer sets for the immunoglobulin heavy-chain locus (IGH*)* complete (IGH-VDJH), IGH incomplete (IGH-DJH), and immunoglobulin κ locus (IGK*).* The amplified product will be subjected to

sequencing, and the sequences and frequencies of the different clonotypes in the sample will be obtained. Myeloma gene rearrangements will be identified. Patients in whom a high-frequency myeloma clone (>5%) is not identified will be excluded from the MRD analysis. MRD will be assessed in patients with a high-frequency myeloma clone using the IGH-VDJH and IGK or IGH-VDJH, IGH-DJH, and IGK assays. Once the absolute amount of total cancer-derived molecules present in a sample will be determined, a final MRD measurement will be calculated, providing the number of cancer-derived molecules per 1 million cell equivalents. In cases in which 2 or more tumor clones existed, the clone with the highest MRD value will be reported. Molecular CR will be defined according to the International Myeloma Working Group (IMWG) consensus recommendations.[56]

11.2.6.2 Modified EBMT Response Criteria

Response	**Criteria for Response[a]**
Complete response (CR)	Requires all of the following: Disappearance of the original monoclonal protein from the blood and urine on at least two determinations for a minimum of six weeks by immunofixation studies. <5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks. [b] No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response).[c] Disappearance of soft tissue plasmacytomas for at least six weeks.
Near Complete Response (nCR)	Requires the following: Same as CR, but immunofixation studies continue to show presence of the monoclonal protein
Very Good Partial Response (VGPR)	Requires the following: ≥ 90% reduction in serum M-protein plus urine M-protein level <100mg per 24 hours on at least two determinations for a minimum of six weeks.

Partial response (PR)	PR includes participants in whom some, but not all, criteria for CR are fulfilled providing the remaining criteria satisfy the requirements for PR. Required all of the following: ≥50% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart. If present, reduction in 24-hour urinary light chain excretion by either ≥90% or to <200 mg for at least two determinations six weeks apart. ≥50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examination) for at least six weeks. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).[c]
Minimal response (MR)	MR included participants in whom some, but not all, criteria for PR were fulfilled, providing the remaining criteria satisfied the requirements for MR. Required all of the following: ≥25% to ≤ 49% reduction in the level of serum monoclonal protein for at least two determinations six weeks apart. If present, a 50 to 89% reduction in 24-hour light chain excretion, which still exceeds 200 mg/24 h, for at least two determinations six weeks apart. 25-49% reduction in the size of plasmacytomas (by clinical or radiographic examination) for at least six weeks. No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).[c]
No change (NC)	Not meeting the criteria for MR or PD.

Response	Criteria for Response[a]
Progressive disease (PD) (for participants not in CR)	Requires one or more of the following: >25% increase[d] in the level of serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed on a repeat investigation. >25% increase[d] in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed on a repeat investigation. >25% increase[d] in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%. Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas. Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture). Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause).

Relapse from CR	Required at least one of the following: Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis confirmed by at least one follow-up and excluding oligoclonal immune reconstitution. ≥5% plasma cells in the bone marrow aspirate or biopsy. Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (not including compression fracture). Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.8 mmol/L not attributable to any other cause).[e]

a Based on the criteria reported by Blade et al., 1998.
b Per Blade *et al*., 1998, if absence of the monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow except in participants with nonsecretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
c Per Blade *et al*., 1998, skeletal X-Rays are not required for the definition of response, but if performed there must be no evidence of progression of bone disease (no increase in size or number of lytic bone lesions).
d It is suggested that the reference point for calculating any increase should be the lowest value of the preceding confirmed response (MR, PR or CR) or the baseline value if there is no previous confirmed response.
e Other clinical data may be requested by the IRC, as necessary, to assess the cause of the hypercalcemia.

11.2.7 Duration of Response and Endpoint Definitions

Duration of overall response: The 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: The duration of overall CR is progression or death. Patients who have not progressed or died are censored at the date last known progression-free.

Time to progression: Time to progression is defined as the time of randomization until progression. Patients who have died without evidence of progression are censored in the TTP analysis at the time of death and patients who are alive without progression are censored at the last disease assessment.

Overall survival (OS): OS is defined as the time from randomization to death. Alive patients are censored at the date last known alive.

11.2.8 Progression-Free Survival

Progression-Free Survival (PFS): the primary endpoint in this study. 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.

11.2.9 Response Review

Central review of disease response assessments is not planned.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 **Data Reporting**

12.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT. Data should be entered within 14 business days of the corresponding visit and within 14 business days of the end of a cycle for any forms to be completed per cycle.

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; 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.

13. STATISTICAL CONSIDERATIONS

13.1 **Study Design/Endpoints**

The primary endpoint of this phase II study is to determine the proportion of high risk

smoldering multiple myeloma (SMM) patients who are progressive free at 2 years after receiving treatment (Elotuzumab + lenalidomide+ Dexamethasone). The secondary objectives include toxicities, objective response rate, time to progression, duration of response, and overall survival. In addition, we will examine the molecular evolution of the tumor cells, the role of circulating tumor cells and immune cells, and the role of NK cells and other immune cells present in the bone marrow in the progression of smoldering MM.

The proportion of patients who achieve progression free at 2 years will be compared to the rate published for the high risk SMM. By the Mayo Clinic model for risk factors, the median time to progression for patients with high risk SMM was only 1.9 years. Therefore, we assume that for this study, a 2-years progression-free rate of 50% will not be considered promising and a true progression free rate of 70% or higher will be considered promising. A single-stage design will be employed with 39 eligible patients entered. If 24 or more of the 39 eligible patients are progression free at 2 years (observed rate of 62%), we will conclude that this treatment warrants further study. The probability of concluding that the treatment is effective if the true rate is 50% is 0.10 and is >0.9 if the true rate is 70%. Assuming an ineligibility rate of 5%, we will accrue 41 patients/per Arm to the trial in order to have 39 eligible patients. A total of 55 patients will be enrolled.

13.1.1 Analysis of Primary Endpoint

Time to progression (TTP) is defined as the time from protocol therapy initiation until documented progression, censored at date last known progression-free for those who have not progressed. At time of final analysis, the 2-year progression-free rate will be estimated using the Kaplan-Meier method with 90% confidence interval per Arm. All patients who have received one dose of study treatment will be included for the TTP analysis, including those who die or are lost to follow-up within 2 years.

The percent of patients who undergo stem cell mobilization and the modality of mobilization will be noted in the study. These patients will not be censored.

13.1.2 Analysis of Secondary Endpoints

The objective response rate (partial response or better according to the modified IMWG criteria) and the proportion of patients with a MRD, CR, PR or MR will be reported by Arm with 90% exact binominal confidence interval (CI). The exact 90% CI around response rate will be no wider than 28% with 39 eligible patients.

To estimate the duration of response (time from objective response to disease progression or death, or date last known progression-free and alive for those who have not progressed or died), progression-free survival (time from protocol therapy initiation to the disease progression or death from any cause, censored at date last known progression free for those who have not progressed or died), and overall survival (time from protocol therapy initiation to death or date last known alive), the Kaplan-Meier method will be used. The results will be reported separately for each Arm.

Safety analysis will be conducted using the Safety Population defined as any patient receiving one dose of study treatment. For toxicity reporting, all adverse events and laboratory abnormalities will be graded and analyzed using CTCAE version 4 as appropriate.

13.2 **Sample Size, Accrual Rate and Study Duration**

A total of 55 patients will be enrolled. We expect 3.5 years of active accrual (approximately 2 patients per month) and 3 years of follow-up of patients.

The final analyses of progression-based endpoints, such as estimating the 2-year progression-free rate and estimating the TTP distribution, will be conducted at the end of the study, which will occur after either all subjects have progressed or died or 2-years after the initiation of therapy of the last subject enrolled, whichever occurs first.

13.3 **Stratification Factors**

The patients will be stratified based on age and cytogenetics.

- Age 65 years or older
- High risk cytogenetics based on t(4:14), t(14:16), 17p deletion or p53 mutation, +1q amplification (3 groups: high risk, low risk or Fish failure)

13.4 **Interim Monitoring Plan**

The study will be monitored by the DFCI Data Safety Monitoring Committee (DSMC). The DSMC will meet at least four times a year and more often if needed (e.g., for safety review). For each meeting, the study will be reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of the outcome data. Copies of the toxicity reports prepared by the DSMC meetings will be distributed to the Principal Investigator. The Principal Investigator will then distribute to sub-investigators. Any DSMC recommendations for changes to the study will be distributed to the Principal Investigator and then circulated to sub- investigators by the Principal Investigator.

13.5 **Stopping Rule for Safety**

All participants will be evaluable for treatment-related toxicity from the time of therapy initiation. The severe adverse event (SAE) is defined as any grade 3 adverse events that affect organ function (cardiac, hepatic, thromboembolic) or grade 4/5 non hematologic AEs. We anticipate that the rate of SAE is low in this study population. However, if 2 or more SAEs are observed at any time in the first 20 treated patients in any study cohort, further patient enrollment will be paused for that cohort.

The following table provides the probabilities of observing 2 or more SAEs with 20 treated participants in each cohort. For example, with 20 participants, there is 0.82 probability of observing 2 or more SAEs if a true rate is 15% and the probability is 0.12 if a true rate is 3%.

True SAE Rate	1%	3%	5%	10%	15%	20%	30%
Probability (≥2 SAEs)	0.017	0.120	0.264	0.608	0.824	0.931	0.992

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 (3) years after the end of the study. Data sets from other relevant studies such as 17-212, 16-313, or data sets from other collaborators may be used and/or analyzed for the purposes of the publication.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: PREPARATION AND ADMINISTRATION OF ELOTUZUMAB

Dose Preparation Instructions

After dilution in normal saline, elotuzumab must be administered within 8 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 the subject's predose weight on Day 1 of each cycle or predose weight at each visit, whichever institutional policy is, and then added to 0.9% saline for infusion. Do not round up or down.

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.

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

Step 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.

Step 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.

Step 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.

Step 5: Once the reconstitution is completed and prior to IV administration, the reconstituted solution is further diluted with 230-340 ml of 0.9% sodium chloride injection (NS), USP, resulting in elotuzumab concentrations between 2 mg/mL and 6.6 mg/mL. The infusion is to be administered through a sterile, non-pyrogenic, low protein binding in-line filter. 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.

The first dose of elotuzumab will be administered following pre-medications to each subject as an IV infusion, using an automated infusion pump set at an initial rate of 0.5 mL per minute (30 mL/hour). If the subject does not have an infusion reaction within 30 minutes, escalate the infusion rate by 0.5 mL per minute. If the subject still does not have an infusion reaction within 30 minutes, escalate the infusion rate to a maximum of 2 mL per minute (120 mL/hour). If a subject experiences a Grade 2 infusion reaction, the infusion must be interrupted.

The second dose of elotuzumab should be initiated at an infusion rate of 3 mL per minute if no infusion reactions were reported with the first elotuzumab infusion. If the subject does not experience an infusion reaction during the first 30 minutes of the second dose of elotuzumab, escalate the infusion rate by 1.0 mL per minute to a maximum infusion rate of 4 mL per minute.

If no infusion reactions were observed during the first two doses cycle of elotuzumab, the third dose can commence at a rate of 5 mL per minute.

If a patient experiences an infusion reaction of less than or equal to Grade 2, and the infusion reaction does not recur, the patient can resume elotuzumab administration at the rate at which the reaction occurred at the start of the next cycle at the investigator's discretion.

If a subject experiences a Grade 2 infusion reaction, the infusion must be interrupted. Please refer to Section 6.4.2 for detailed information on the management of infusion reaction and re-initiation of infusion. If a subject experiences a Grade 3 elotuzumab infusion reaction that has resolved to Grade 1, subsequent infusion rate of elotuzumab should be escalated in a stepwise fashion (0.5 mL every 30 minutes).

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 0.5mL 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.

The elotuzumab infusion rate will be increased gradually to a maximum of 5 mL/min as presented in the table below. The schedule below will be permitted only if no infusion reactions are encountered. For guidance related to elotuzumab infusion reactions, refer to section 6.4.

Cycle/Day	Infusion Rate	Duration of Infusion	Approximate Total Infusion Time
Cycle 1 Day 1 (10mg/kg)	0.5 mL/min	30 minutes	2 hours and 50 minutes
	1 mL/min	30 minutes	
	2mL/min	110 minutes	
Cycle 1 Day 8 (10mg/kg)	3 mL/min	30 minutes	1 hour and 13 minutes
	4 mL/min	43 minutes	
Cycle 1 Day 15 and 22 And Cycle 2-8 (10mg/kg)	5mL/min	53 minutes	53 minutes
Cycle 9-24 (20mg/kg)	5mL/min	81 minutes	81 minutes

APPENDIX C: 14-338 SPECIMEN COLLECTION SCHEDULE

Sample Time Point	Recipient	Sample Type	Shipping Method	Container[1,2]
Baseline	DFCI	Peripheral Blood	Fridge pack same day	3x 10mL Purple Top 1x6ml Red Top
		Bone Marrow Aspirate		2x10mL Purple Top
		Buccal Swab[2]	Ambient same day	1x Buccal Swab Kit
	Sequenta	Bone Marrow Aspirate	Same day – Use kit provided	1x3ml Purple
Cycle1 Day 1 (Pre Dose)	DFCI	Peripheral Blood	Fridge pack same day	2x10mL Purple Top 1x6ml Red Top
Cycle 2-8 Day 1 (Predose)	DFCI	Peripheral Blood	Fridge pack same day	2x10mL Purple Top[3] 1x6ml Red Top
End of Cycle 8 (Cycle 9 Day 1)	DFCI	Peripheral Blood	Fridge pack same day	2x 10mL Purple Top[3] 1x6ml Red Top
		Bone Marrow Aspirate		2x10mL Purple Top[3]
Cycle 10-24 Day 1 (Predose)	DFCI	Peripheral Blood	Fridge pack same day	2x10mL Purple Top 1x6ml Red Top
Confirm Complete Response [4]	DFCI	Peripheral Blood	Fridge pack same day	2x 10mL Purple Top 1x6ml Red Top
		Bone Marrow Aspirate		2x10mL Purple Top
	Sequenta	Bone Marrow Aspirate	Same day – Use kit provided	1x3ml Purple Top
End of Treatment and/or Disease Progression	DFCI	Peripheral Blood	Fridge pack same day	2x 10mL Purple Top 1x6ml Red Top
		Bone Marrow Aspirate		2x10mL Purple Top
Clinically Indicated/ **and/or Yearly Bone Marrow Biopsy/Aspirate**	DFCI	Bone Marrow Aspirate	Fridge pack same day	2x10mL Purple Top[3]
		Peripheral Blood		

[1] Purple Top= K2EDTA Tube; Red Top= No Additive; Sequenta Tubes= Provided by Sequenta/Lead Site
[2] Buccal Swabs will be provided by the lead site, and can be sent at any time point during the trial
[3] Samples at these time points are voluntary, and do not exclude patients from treatment
[4] For definition of Complete Response, please refer to section 11.2.3.

APPENDIX D: 14-338 SPECIMEN REQUISITION

Complete this form and include with the specimen shipment. Label all materials with DFCI participant study ID, collection time point and collection date and time. Email GhobrialLab@dfci.harvard.edu to alert study team of shipment and include tracking number.

Ship specimen(s) to:

Dana Farber Cancer Institute
Ghobrial Lab
360 Longwood Avenue LC8116
Boston, MA 02215

Specimen Information

DFCI Participant Study ID Number: _____ Date specimen(s) shipped: _____

Correlative Sample Time Points *(indicate inclusion in shipment by checking box)*	**Sample Type**	**Quantity of Tubes (6ml or 10ml)**	**Collection Date**	**Collection Time**
☐ Pre-treatment/Baseline	☐ Blood ☐ Aspirate ☐ Swabs	_____Red Top Purple Top		
☐ Cycle 1-24 Day 1 Specify Cycle_____	☐ Blood	_____Red Top Purple Top		
☐ Confirm Response	☐ Blood ☐ Aspirate	_____Red Top Purple Top		
☐ Cycle 9 Day 1 (end of Cycle 8)	☐ Blood ☐ Aspirate	_____Red Top Purple Top		
☐ End of Treatment ☐ Disease Progression	☐ Blood ☐ Aspirate	_____Red Top Purple Top		
☐ Clinical Necessity/ Standard of Care	☐ Aspirate	_____Purple Top		

Responsible Contact: _____ **Email:** _____

Site: _____ **Phone number:** _____

Note: All samples are to be shipped with a fridge pack Fed-Ex priority overnight- Please retain a copy of the waybill, and reference the tracking number in the email and paper correspondence. Ship ***only Monday- Thursday***, as shipments cannot be received over the weekend

DFCI IRB Protocol #: 14-338

APPENDIX E: DF/HCC MULTI-CENTER DATA AND SAFETY MONITORING PLAN

TABLE OF CONTENTS

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 (CTEP, 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 (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) 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 (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Quality Assurance Office for Clinical Trials: A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. QACT also coordinates quality assurance efforts related to multi-center clinical research.

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, **Irene Ghobrial, 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.
- 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.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC QACT.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions 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 plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain 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
- 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 Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC 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.

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

3.7.1 Participant Registration

See **Sections 4.3 and 4.4** of the protocol.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC QACT 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 QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, QACT 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 **Section 7** of the protocol.

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 QACT develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC QACT 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 QACT 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 re-submitted 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 QACT and distributed on a monthly basis.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in **Section 8** of the protocol.

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 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 QACT provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Also, the Participating Institution may be subject to on-site monitoring conducted by the DF/HCC Lead Institution.

The DF/HCC Lead Institution will implement on-site as well as virtual monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. At a minimum, the DF/HCC Lead Institute, or designee, will monitor each participating site twice a year while patients are receiving treatment. Should a Participating Institution be monitored once and then not accrue any additional patients or participant visits, then a second monitoring visit may not be necessary.

Monitoring practices may 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 records and site trial master files, protocol deviations, pharmacy records, response assessments, and data management. Additionally, regular and ongoing communication with Participating Institutions will be accomplished by holding all site teleconferences at least monthly. The Lead Institution will keep in close touch with the Participating Institutions via email and phone. Source documents from Participating Institutions, will be collected at specific data points that support the primary and or secondary endpoints.

On-Site Monitoring: On-site monitoring will occur at least once per year. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled. On site monitoring visits can be supplemented with virtual monitoring assessments, provided that the minimum monitoring frequencies are adhered to.

Virtual Monitoring: The Coordinating Center will request source documentation from Participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

5.2 Monitoring Reports

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. 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. Due to the small patient population, the accrual minimum requirement is at least 1 patient every two years.

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: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the QACT, assuming at least three participants have been treated on protocol at the site, or at the discretion of the DF/HCC sponsor. 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.

6.2 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. 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.

6.3 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 QACT 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.

6.4 Participating Institution Performance

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

6.4.1 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.