Protocol Title:

Phase II Trial of the PD-1 Antibody Nivolumab in Combination with Lenalidomide and Low Dose Dexamethasone in Patients with High-Risk Smoldering Multiple Myeloma

NCT #: NCT02903381

IRB Approval Date: 01/23/2018

Local Protocol #:16-242
BMS Protocol #: CA209-607

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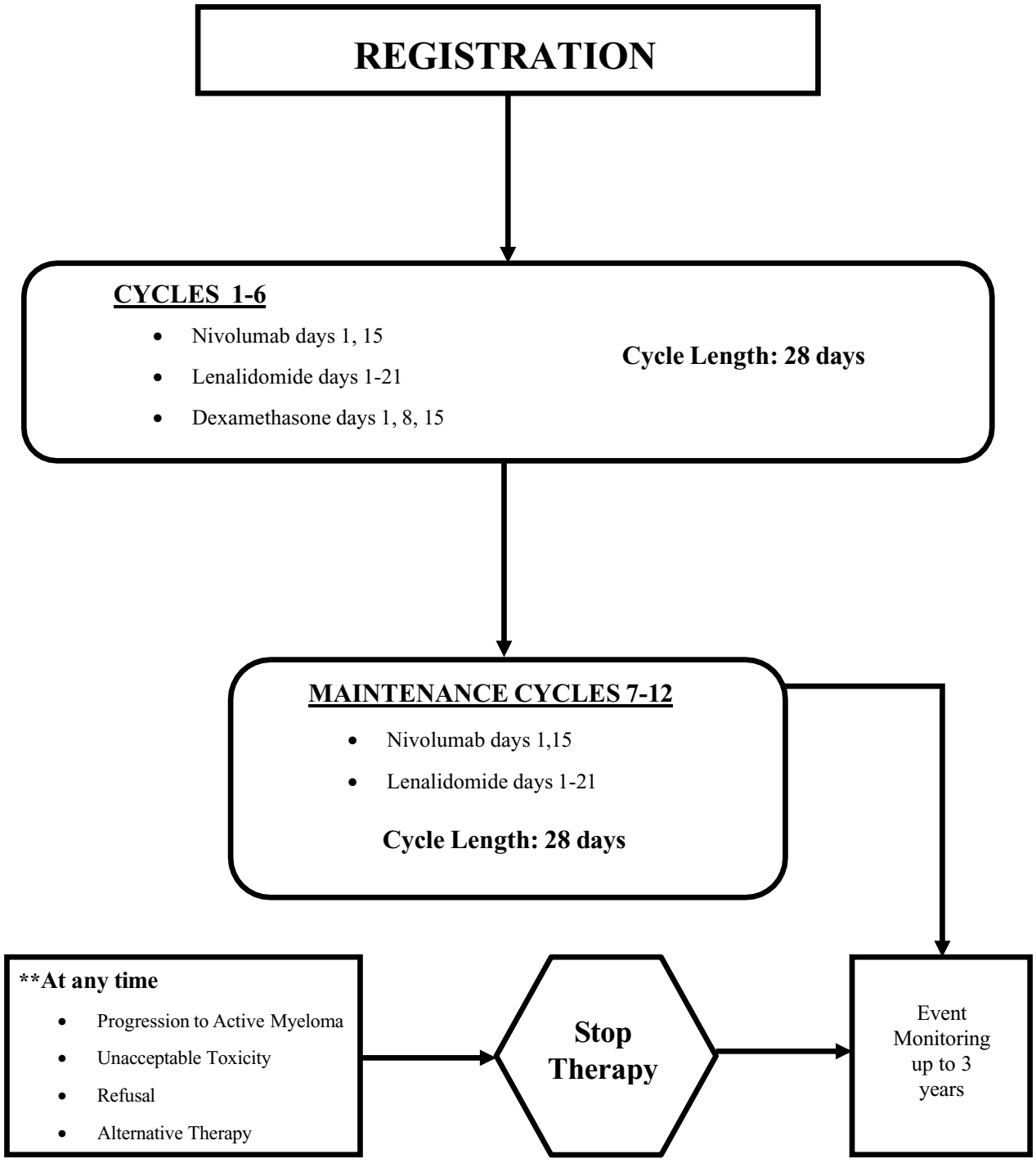
Agent(s): Nivolumab, Bristol-Myers Squibb
Lenalidomide, Celgene
Dexamethasone, commercial

IND #: 129255
IND Holder: Irene M. Ghobrial, MD

Original/ 11.0/ January 23rd 2018

SCHEMA



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

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
Ara-C	Cytarabine
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZD	Benzodiazepines
CBC	complete blood count
CFR	Code of Federal Regulations
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system

Abbreviation	Term
CO_2	carbon dioxide
CR	complete remission
CRM	continual reassessment method
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	coefficient of variation
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus

Abbreviation	Term
HNSTD	highest nonseverely toxic dose
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K_i	inhibition constant
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen

Abbreviation	Term
QD	*quaque die*; each day; once daily
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

PROTOCOL SUMMARY

Study Title: Phase II Trial of the PD-1 Antibody Nivolumab in Combination with Lenalidomide and Low Dose Dexamethasone in Patients with High-Risk Smoldering Multiple Myeloma

Phase: II

Number of Patients: 41

Study Objectives:

Primary Objectives

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

Secondary Objectives

- To assess the response rate of the combination in these patients
- To assess time to progression and progression free survival
- To assess duration of response
- To assess the 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)

Overview of Study Design:

This is a single arm phase II study using the combination of Nivolumab and lenalidomide + low dose dexamethasone in patients with high risk smoldering multiple myeloma. The study is designed to examine novel therapeutic immunotherapy combinations in patients with smoldering MM. The trial will include a safety run in of 10 patients. If three of the ten patients experience a serious, unexpected adverse event during their first cycle of therapy, the study will be suspended temporarily until further safety review.

Study Population:

SELECT INCLUSION CRITERIA

- Age ≥ 18 years.
- 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 ≥3.0g/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

* 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.

- High risk cytogenetics or FISH including t (4;14) or del 17p or 1q gain
- Increased circulating plasma cells
- MRI with diffuse abnormalities or 1 focal lesion
- PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

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

- No evidence of CRAB criteria* or new criteria of active MM which including the following:
  - Increased calcium levels (corrected serum calcium >0.25 mmol/dL {1mg/dL) above the upper limit of normal or >2.75 mmol/dL {11mg/dL});
  - Renal insufficiency (attributable to myeloma);
  - Anemia (Hb 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 (*except for light chain smoldering MM)

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

- ECOG Performance Status (PS) 0, 1, or 2.
- The following laboratory values obtained ≤ 21 days prior to registration:
  - ANC ≥ 1000/μL
  - PLT ≥ 50,000/μL
  - Total bilirubin ≤ 1.5 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)

SELECT EXCLUSION CRITERIA

- Symptomatic Multiple Myeloma or any evidence of CRAB criteria. Any prior therapy for Multiple Myeloma should also be excluded Bisphosphonates are not excluded. Patients who received prior therapy due to being incorrectly diagnosed as having overt multiple myeloma may not be excluded after discussion with the overall PI.
- 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.
- Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune pneumonitis, autoimmune vasculitis [eg, Wegener's Granulomatosis]) and motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia, Gravis). Patients with Hashimoto's thyroiditis are eligible to go on study. The Overall PI must be consulted to discuss any other autoimmune disorders not listed here to determine if the patient is eligible for the trial.

Duration of Study: 5 years

1. OBJECTIVES

Smoldering Multiple Myeloma (SMM) is a heterogeneous disease entity that includes patients who have a disease burden that is higher than that in patients with MGUS but who are not yet symptomatic[1]. The term SMM was first described by Greipp and Kyle et al in 1980[2] and was followed by many other descriptions terming it indolent MM[3], or Durie Salmon Stage I[4]. It was not until 2003 that the International Myeloma Working Group (IMWG) described the exact definition of this disease. SMM was defined as serum M-protein ≥3 g/L and/or ≥10% monoclonal plasma cells in the bone marrow (BM), Table 1[5,6]. While the incidence and prevalence of SMM in the population is not well defined, it has been estimated to represent approximately 8% to 20% of patients within the MM spectrum[1].

Most recently, the IMWG further re-defined the group of patients who meet criteria for treatment and included asymptomatic SMM patients who are likely going to have end-organ damage in the near future, previously defined as "ultra-high risk smoldering myeloma". These include patients with bone marrow plasmacytosis ≥60% [7]; an abnormal FLC-ratio ≥100 (involved kappa) or <0.01 (involved lambda) [8]: and/or 2 or more focal bone marrow lesions detected by functional imaging including PET-CT and/or MRI [9,10]. These patients should therefore not be considered SMM anymore but rather re-defined as patients with myeloma-defining events that require therapy.

The overall risk of progression of SMM is 10% per year for the first 5 years and 3% per year for the next 5 years[11]. The most common factors used to stratify patients with SMM are the Mayo Clinic criteria[11,12] and the Spanish PETHEMA criteria[13]. The Mayo Clinic criteria are based on the tumor burden defined by the serum protein level (by serum protein electrophoresis or light chain ratio) or by the percent bone marrow plasma cell involvement (see Table 2)[11,12], leading to risks of progression at 5 years of 25% for low risk, 51% for intermediate risk and 76% for high risk individuals who have 1, 2 or 3 risk factors respectively[11,12]. The risk stratification of the PETHEMA group is based on identifying the number of clonal plasma cells in the bone marrow by flow cytometry (≥95% ratio of abnormal neoplastic plasma cells to normal plasma cells) and reduction of uninvolved immunoglobulins, with 5 year-risk of progression being 4%, 46%, and 72% for patients with 0, 1 or 2 risk factors, respectively[13].

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)[14-16]. 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[17]. Therefore, there is a need to examine novel therapeutic combinations in patients with high risk smoldering 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 nivolumab and lenalidomide in patients with high-risk SMM.

1.1 Study Design

This is a phase II study using the combination of Nivolumab and lenalidomide + low dose dexamethasone in patients with high-risk smoldering multiple myeloma. The trial will include a safety run in of 10 patients. If three of the ten patients experience a serious, unexpected adverse event during their first cycle of therapy, the study will be suspended temporarily until further safety review. If any one of the study medications is permanently discontinued for any reason including toxicity, or FDA mandate, the patient may remain on the study at the discretion of the principal investigator.

** As of September 2017, the trial has been put on partial clinical hold by the Food and Drug Administration: all patients are to discontinue nivolumab indefinitely, and no additional patients will be accrued to the trial. Participants may elect to remain on lenalidomide/dexamethasone or lenalidomide therapy alone for disease control after discussion with the overall PI.

1.2 Number of Patients

A total of 41 patients will be included on this study. Enrollment includes patients who receive the first day of therapy.

1.3 Duration of Study

A treatment cycle is defined as 28 consecutive days.

Patients will receive 6 cycles of induction therapy followed by 6 cycles of maintenance therapy with lower doses of lenalidomide and no dexamethasone for a total of 12 months.

During maintenance, if a patient experiences biochemical progression (≥ 25% increase and an absolute increase of ≥ 0.5g/dL from their nadir in their serum or urine m-spike or FLC with no CRAB features attributable to MM progression) high-dose dexamethasone may be re-added to the combination at a dose of 40mg oral given on days 1, 8, and 15 of a 28 day cycle after discussion with the overall PI.

For all treatment cycles a +/- 7 day window is allowed for Nivolumab. For hold and delay guidelines for lenalidomide and dexamethasone, please refer to Table 17. The treatment plan is designed to be administered on an outpatient basis, however if necessary, may be given as inpatient.

Patients will be followed for up to three years after discontinuation of therapy.

1.4 Primary Objectives

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

1.5 Secondary Objectives

- To assess the response rate of the combination in these patients
- To assess time to progression and progression free survival
- To assess duration of response
- To assess the safety and tolerability 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) by Adaptive's LymphoSIGHT sequencing platform.

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 [18]. 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 [19]. Smoldering multiple myeloma was defined by the presence of serum M-protein ≥ 3 g/dL or IgA> 2g/ dL or urinary monoclonal protein > 500 mg/ 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 [20]. 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%) [21]. 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 [11,12]. 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.[7]

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[22]. 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 [23].

2.3 Molecular studies in MGUS and SMM

A recent study using SNP-based arrays compared MGUS, SMM and MM samples [24]. 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 [25]. 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 [26]. 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 [25,26]. The mir17 cluster has been shown to upregulated by the transcription factor c-Myc, which is considered a late event in myeloma progression [27-29].

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 [30]. 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[31-35]. 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[24,36,37].

2.4 Definition of SMM and MM

The diagnosis of smoldering (asymptomatic) multiple myeloma (SMM)[38,39] is based on:

- Serum monoclonal protein (IgG, IgM, IgD or IgA) ≥3 g/dL or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells (BPMC) 10–60%.
- Absence of myeloma defining events or amyloidosis
- No evidence of the following CRAB criteria or other Myeloma defining events (MDE):
    - Increased calcium levels (corrected serum **calcium** >0.25 mmol/dL above the upper limit of normal or >2.75 mmol/dL) related to MM
    - **Renal** insufficiency (attributable to MM)
    - **Anemia** (Hb 2g/dL below the lower limit of normal or <10g/dL) related to MM
    - **Bone** lesions (lytic lesions or generalized osteoporosis with compression fractures)

New MDE criteria that indicates overt MM and not SMM[38,39]

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 plasma cells >60%
- Serum involved/uninvolved FLC ratio ≥100mg/L, provided the absolute level of the involved free light chain is at least 100 mg/L and repeated twice (except for monoclonal light chain smoldering MM and for those with stable serum light chains for 6 months.)
- MRI with two or more focal lesion that is at least 5 mm or greater in size

2.5 Definitions of High-Risk SMM

Based on the new defined high risk criteria for smoldering myeloma based on [40] as described in table 3 below:

Table 3 Bone marrow clonal plasma cells ≥10% and any one or more of the following:
Serum M protein ≥3.0g/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
PET-CT with focal lesion 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

2.6 Treatment of high risk SMM

In a randomized open-label phase 3 trial [17], 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 Nivolumab

2.7.1 Preclinical Experience

Please refer to the current nivolumab Investigator's Brochure (IB) and Safety Management Attachment located in Appendix D

2.7.2 Clinical Experience

Nivolumab is a fully human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cell surface membrane receptor. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro.

Nivolumab has demonstrated clinical activity as monotherapy in subjects with a variety of malignancies including lung, melanoma, renal cell carcinoma and in lymphomas, responses have been reported for diffuse large B-cell lymphoma, follicular lymphoma, and Hodgkin's

lymphoma. (See IB for details).

Approximately 4,000 subjects have received nivolumab monotherapy in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti angiogenics, and targeted therapies). The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, the frequency of AEs may be greater than that observed with either agent alone. For nivolumab monotherapy and combination therapy, most high-grade events were manageable with use of corticosteroids or hormone replacement therapy.

2.8 Pharmacokinetics and Drug Metabolism

2.8.1 Flat Dose Regimen

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to 3 mg/kg Q2W dosing regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight in nivolumab clinical trials. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Hence, a flat dose of 240 mg nivolumab is under investigation.

2.8.2 Shorter Infusion Duration

Establishing that nivolumab can be safely administered using a shorter infusion time (30 minutes) is under investigation. Previous clinical studies of nivolumab monotherapy have used a 60-minute infusion duration wherein, nivolumab has been safely administered up to 10 mg/kg over long treatment periods. Infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical program. In CA209010, a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1-2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab.

Additional information on the background and development of nivolumab can be found on the Nivolumab Investigator's Brochure.

2.9 Trial Rationale

Based on the activity of lenalidomide and dexamethasone in patients with SMM and based on the data that progression of tumors is based on evasion and suppression of the host immune system, we believe that the combination of a PD-1 inhibitor with lenalidomide will induce high responses and delay development of symptomatic MM in patients with high risk Smoldering MM.

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.

2.9.1 Dexamethasone effect on immune response

The use of dexamethasone in this study may blunt the immune response to Nivolumab. However, all prior studies of lenalidomide and dexamethasone in smoldering myeloma have used the combination of both agents. Therefore, to assess the true significance of adding Nivolumab to this combination, we will not omit dexamethasone from the regimen. In addition, recent studies in MM have shown that pulse dexamethasone used in our regimens of myeloma does not significantly blunt the immune response[41]. Moreover, recent studies in relapsed myeloma have shown preliminary strong activity of immune-mediated antibodies in combination with lenalidomide and dexamethasone. Moreover, we will monitor for immune cell numbers and checkpoint regulation on immune cells at the start of therapy and during therapy to define the effect of these agents on immune regulation. If patients cannot tolerate dexamethasone, then dose reductions will be permitted as described in dose reduction/modification sections.

2.9.2 Stem Cell Mobilization and Collection

Patients who are eligible for stem cell collection and who intend to go on to transplant will have the option to collect stem cells during the course of therapy on this trial at the time of best response (PR,VGPR, or CR or at investigator's discretion) or after 6 cycles of induction therapy, however, collection may be done at any time during the study after discussion with the Overall PI. Institutional guidelines should be followed in regards to stem cell mobilization and collection. Patients should be mobilized as soon as possible after stopping study treatment. Patients may delay resuming treatment for up to 3 weeks after collection is complete.

Plerixafor should be utilized as a mobilization agent primarily; however cyclophosphamide or other agents may be used at the investigator's discretion. Based on data using combination therapies for induction, there have been no major concerns regarding stem cell collections after treatment with these agents.

2.10 Correlative Studies Background

2.10.1 DNA and RNA sequencing of tumor cells

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[42,43]. The genomic complexity in MM was recently corroborated by massive parallel-sequencing studies displaying the lack of a universal driving mutation[30]. Recent studies have shown intraclonal heterogeneity that occurs at different stages of progression in MM[31,32]. 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[44,45]. Point mutations such as N-RAS, K-RAS, MYC up-regulation[46], and gain or loss of chromosome 1q or 1p seem to correlate with disease progression from MGUS and SMM[29]. A progressive increase in the incidence of copy number abnormalities from MGUS to SMM and to MM has been recently observed[47].

We plan to perform exome sequencing and RNA sequencing studies on tumor cells obtained at the time of screening as well as from subsequent bone marrow biopsy samples to examine clonal heterogeneity, resistant clones at best response and at time of end of study or tumor progression. The hypothesis is that clonal evolution and the progression/response of different clones in response to immunotherapy would be critical to better understand clonal evolution in MM and help in the development of future therapeutic options for patients with MM.

The tumor research samples will be collected at the time of scheduled bone marrow biopsies. From these samples, high quality DNA (for tumor cells) and RNA for both exome sequencing and RNA sequencing will be obtained. In brief, BM aspirates will be obtained after informed consent. The tumor cells will be collected using CD138+ bead selection (over 90% purity based on prior publications)[30,31]. For samples that have a small fraction of plasma cells, we will use flow sorting for CD138/CD38/CD56 and CD19-ve to obtain a pure malignant plasma cell population based on prior published markers of malignant plasma cells[48]. Germline DNA will also obtained from a buccal swab from all patients.

2.10.2 Exome sequencing of tumor cells

Whole-exome capture libraries will be constructed from 100ng of tumor and normal DNA followed by shearing, end repair, phosphorylation and ligation to barcoded sequencing adapters. The DNA will be size-selected to exonic hybrid capture using SureSelect v2 Exome bait (Agilent, CA). Samples will be multiplexed and sequenced on Illumina HiSeq flowcells with the goal of an average depth of coverage of 100x. The resulting data will be analyzed with the current Illumina pipeline, which generates data files (BAM files). The details of the current analysis pipeline are published elsewhere[30,49]. Briefly, somatic single nucleotide variants are determined using the MuTect algorithm[50]. Indels and translocations are determined by the algorithms IndelLocator and dRanger, respectively. The MutSig algorithm identifies genes in which the observed mutations are inconsistent with what would be expected at random[51]. To accurately assess the significance of mutations, MutSig takes into account several covariates, which influence the background mutation model. These include the expression level of genes (for which published gene expression data of MM samples can be used), and other gene characteristics observed empirically to co-vary with mutation rate: local relative replication

time[52], and open vs. closed chromatin status[53]. Focal as well as arm-level copy number variations will be determined based on whole exome sequencing and subsequent application of the GISTIC algorithm[54].

2.10.3 RNA sequencing of tumor cells.

For RNA Sequencing, poly-A selection and cDNA synthesis will be performed, followed by library preparation, sequencing (76bp or 101bp paired reads), and sample identification with quality control. Details of experimental design are described in[55,56-58]. We will perform library construction using a non-strand specific Illumina TruSeq Protocol and sequence coverage to 100M total reads. Analysis will be performed as described in the preliminary data and in previous studies[56-58].

2.10.4 Immune cell characterization in peripheral blood and bone marrow

Peripheral blood and bone marrow derived mononuclear cells will undergo immunologic assessments to assess the impact of therapy on general measures of cellular immunity. We will determine the number of immune cells (T-regs, CD4 effector T cells, CD8 T-regs, CD8 effector T cells, NK, NKT, B cells, MSCs, M1 and M2 macrophages, Dendritic cells and MDSCs at screening and during therapy. These cells will be quantified using CyTOF. Each cell type will be defined by unique combinations of antibodies based on previous publications[59,60]. Regulatory T cells will be defined as CD4/CD25/FOXP3+ cells. Levels of naïve, effector and central memory cells will be quantified as CD45RA, CD45RO/CD62L-/CD27- and CD45RO/CD62L+/CD27+ cells, respectively. NK cells will be quantified by expression of CD56+ subsets. MDSCs will be quantified by CD33+/lineage-/DR- and CD11b/lineage-/DR- cells. We will also examine the percent expression of checkpoint regulators and how they are modulated with therapy. These checkpoint regulators include PD-1, Lag-3, Tim-3 and CTLA-4.

2.10.5 RNA sequencing of immune cells during therapy

We will dissect molecular alterations that occur in these cells during progression in MM and the role of therapy on these cells. We will obtain the T-regs, NK cells and MDSCs from the peripheral blood and bone marrow at the same time points described above. Similar samples will be obtained from the comparative untreated cohort. The cells will be isolated by flow sorting using single cell sequencing and submitted for RNA sequencing as described above. Single cell sequencing of immune cells has recently shown significant advances in understanding immune regulation of the tumor microenvironment. Therefore, we believe that these studies will help define the immune microenvironment in smoldering MM before and after therapy with a PD-1 inhibitor.

2.10.6 Cell free DNA to monitor genomic evolution

Human cancers are caused by the accumulation of genetic alterations in cells. Of special importance is the sequence at which the genetic events arise, as early events likely result in common oncogenic dependency that represents favorable therapeutic targets. Non-invasive liquid biopsies, by means of circulating tumor cells (CTC) and circulating free DNA (cfDNA),

facilitate the continuous monitoring of genomic evolution. CTCs have been identified in solid tumors as well as in multiple myeloma (MM). Likewise, massive parallel sequencing of cfDNA has been shown to track genomic evolution of several types of cancer during the course of the disease. This could potentially complement current invasive biopsy approaches and constitute a new paradigm for monitoring clonal evolution in human cancers and provide the possibility for an early detection of known MM driver mutations that could predict risk of progression. CfDNA sequencing can be challenging because of the small fragment size of DNA in the peripheral blood (around 166bp), the low yield of DNA and the usual low allelic fraction of tumor-derived DNA among the cfDNA. Therefore, we developed two different approaches to sequence cfDNA. After high-speed centrifugation of frozen samples, to eliminate residual cells from plasma, cfDNA is extracted using the Qiagen circulating nucleic acid kit. As little as 5ng of cfDNA is then subjected to library preparation using the Kapa HyperPlus kit, which enables us to prepare libraries from small DNA fragments and minimal DNA yield. CfDNA libraries are qualified for further sequencing using ultra-low-pass whole genome sequencing (ULP-WGS). The ULP-WGS is a low cost approach developed by the Blood Biopsy Group to nominate samples containing sufficient fraction of tumor-derived DNA for whole exome sequencing (WES). Large numbers of cfDNA libraries are multiplexed and sequenced to an average of 0.1X genome-wide sequencing coverage. Samples with lower than 5% purity, not suitable for WES, are analyzed by a targeted deep sequencing approach for cfDNA to increase the sensitivity of detection of low allelic fraction mutations. Our custom amplicon set includes 109 genes exons to detect single nucleotide variants (SNVs). WES and targeted libraries are then sequenced on a HiSeq 4000. Mutations are called using MuTect in single-sample mode. All known germline variants are filtered out (1000 Genome Project Consortium release 2.2.2) and somatic SNVs are characterized for their presence in the Catalogue of Somatic Mutations in Cancer (COSMIC) database. All somatic SNVs are reviewed manually with Integrative Genomic Viewer (IGV) to validate their accuracy. We assess the reproducibility of our assay by running samples in duplicates, which show a high correlation between the 2 replicates in the same test run.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Age ≥ 18 years.

3.1.2 Must meet criteria of high risk smoldering MM based on the criteria described below:

Definition of high-risk SMM:

- Bone marrow clonal plasma cells ≥10% and ≤60% **and any one or more of the following:**
  - Serum M protein ≥3.0g/dL (IgA, IgG, IgM, or IgD)
  - 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)
    - Increase in serum monoclonal protein by ≥10% on two successive evaluations within a 6 month period
- 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
- PET-CT with one focal lesion with increased uptake without underlying osteolytic bone destruction
- Urine monoclonal light chain excretion ≥500 mg/24 hours

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

3.1.4 The following laboratory values obtained ≤ 21 days prior to registration and confirmed prior to the first dose of study drug:

- ANC ≥ 1000/μL
- PLT ≥ 50,000/μL. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
- Total bilirubin ≤ 1.5 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)
- WBC ≥2000/μL

3.1.5 Ability to understand and willingness to sign a 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.

3.1.6 Female patients who are postmenopausal for at least 1 year before the screening visit or are surgically sterile. Females of childbearing potential* must have a negative serum or urine pregnancy test with a sensitivity of at least 25 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. Females of reproductive potential must agree to follow instructions for method(s) of contraception for the duration of treatment with any study drug(s) plus 5 half-lives of study plus 30 days (duration of ovulatory cycle) for a total of 120 days after their last dose of lenalidomide (Revlimid). Women must not breastfeed.

Female patients who are of childbearing potential must use contraception for 5 half-lives plus 30 days after their last dose of nivolumab for a total of 5 months.

** 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)*

3.1.7 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.

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

3.1.9 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 during the entire study treatment period and through 154 days after the last dose of lenalidomide (Revlimid) or agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Men who are sexually active with women who are of childbearing potential must adhere to contraception for a period of 5 half-lives plus 90 days for a

total of 7 months after their last dose of nivolumab.

3.2 Exclusion Criteria

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

- Increased calcium levels (corrected serum calcium >0.25 mmol/dL {>1mg/dL} above the upper limit of normal or >2.75 mmol/dL {11mg/dL}) related to MM
- Renal insufficiency (attributable to MM)
- Anemia (Hb 2g/dL below the lower limit of normal or <10g/dL) related to MM
- Bone lesions (lytic lesions or generalized osteoporosis with compression fractures)
- Bone marrow plasma cells >60%
- Serum involved/uninvolved FLC ratio ≥100, provided the absolute level of the involved free light chain is at least 100 mg/L and repeated twice (light chain smoldering myeloma as described in section 2.4 is not an exclusion criteria).
- MRI with two or more focal lesions that are at least 5 mm or greater in size

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

3.2.2 Other concurrent chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered investigational. Prior therapy with bisphosphonate is allowed. Prior therapy for smoldering myeloma MM may not be an exclusion criterion, discussion with Principal Investigator must occur before enrolling patients with prior treatments. Prior radiation therapy to a solitary plasmacytoma is allowed. Patients who received prior therapy due to being incorrectly diagnosed as having overt multiple myeloma may not be excluded after discussion with the overall PI.

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 Autoimmune disease: Patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's Disease, are excluded from this study, as are patients with a history of symptomatic disease (eg, rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, autoimmune pneumonitis, autoimmune vasculitis [eg, Wegener's Granulomatosis]) and motor neuropathy considered of autoimmune origin (e.g. Guillain-Barre Syndrome and Myasthenia, Gravis). Patients with Hashimoto's thyroiditis are eligible to go on study.

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

3.2.8 History of severe allergic reactions attributed to compounds of similar chemical or biologic composition to Nivolumab or lenalidomide.

3.2.9 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.

3.2.10 Major surgery within 4 weeks of enrollment.

3.2.11 Myeloma-related central nervous system involvement.

3.2.12 Known Amyloid involvement.

3.2.13 Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

3.2.14 Prior CVA with persistent neurological deficit.

3.2.13 Inability to tolerate thromboprophylaxis.

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

The Research Project Manager will enter eligible participants on study at DFCI. All sites should call or email the Research Project Manager, to ensure enrollment availability prior to consenting any patients.

Following registration, participants should begin protocol therapy as soon as feasible. 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 Research Project Manager 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

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 Research Project Manager will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration

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

NOTE: Registration with the coordinating center 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 study team at DFCI.

5. TREATMENT PLAN

5.1 Treatment Regimen

Treatment will consist of 6 cycles of induction therapy followed by maintenance therapy for a total of 12 months. A treatment cycle is defined as 28 consecutive days.

For treatment cycles 1 through 12, a +/- 7 day window for nivolumab dosing is allowed
For further guidance on lenalidomide and dexamethasone holds and delays, please see Table 17.
No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

** As of September 2017, the trial has been put on partial clinical hold by the Food and Drug Administration: all patients are to discontinue nivolumab indefinitely, and no additional patients will be accrued to the trial. Participants may elect to remain on lenalidomide/dexamethasone or lenalidomide therapy alone for disease control after discussion with the overall PI.

Induction Cycles

Table 7: Nivolumab and Lenalidomide and Dexamethasone Combination (Cycles 1-6)

Agent	Pre-medications/ Precautions	Dose	Route	Schedule	Cycle Length
Nivolumab	None	240 mg	Intravenous	Days 1,15	28 days
Lenalidomide	None	25 mg	Oral	Days 1-21 of each cycle	
Dexamethasone	Take with food; Recommended to be taken in the morning	40 mg	Oral	Days 1, 8, 15	

Maintenance Cycles**

Table 8: Nivolumab and Lenalidomide Combination (Cycles 7-12)

Agent	Pre-medications/ Precautions	Dose	Route	Schedule	Cycle Length
Nivolumab	None	240 mg	Intravenous	Days 1, 15	28 days
Lenalidomide	None	15 mg*	Oral	Days 1-21 of	

				each cycle	

* If patient was dose reduced during the induction phase for lenalidomide below 15mg, then maintenance phase starts at that dose reduction and not at the higher 15 mg dose.

** During maintenance, if a patient experiences biochemical progression (≥ 25% increase and an absolute increase of ≥ 0.5g/dL from their nadir in their serum or urine m-spike or FLC with no CRAB features attributable to MM progression) high-dose dexamethasone may be re-added to the combination at a dose of 40mg oral given on days 1, 8, and 15 of a 28 day cycle after discussion with the overall PI.

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

5.2 Agent Administration

The drugs may be administered in any order.

5.2.1 **Nivolumab**

5.2.1.1 Administration

Nivolumab will be administered at a dose of 240 mg as an intravenous infusion over 60 minutes (+/- 10 minutes) every 2 weeks (Days 1 and 15 of each 28 day cycle).

See section 8.1.7 for guidelines on drug preparation and section 8.1.8 for further guidelines for drug administration.

Administer the infusion over 60 minutes (+/- 10 minutes) through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not co-administer other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

5.2.1.2 Dose Delay or Interruption

Please refer to section 6.2 of the protocol.

5.2.2 **Lenalidomide**

Lenalidomide will be obtained from commercial supply in this study. This may lead to added costs for the participant or the participant's insurance company.

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 induction (cycles 1-6) and 15 mg per day on days 1-21 for maintenance (cycles 7-12) (if a patient was dose reduced during the induction phase for lenalidomide below 15mg, then maintenance phase starts at that dose reduction and not at the higher 15 mg dose). Please refer to Table 17 for specific hold and delay instructions for lenalidomide. Dose modification guidelines are described in Section 6.3.

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 may 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 must 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 6.3).

Lenalidomide related resources must 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.

5.2.2.1 Dose Delay or Interruption

Please refer to section 6.3 of the protocol.

5.2.3 **Dexamethasone**

Dexamethasone will be obtained from commercial supply in this study. This may lead to added costs for the participant or the participant's insurance company.

Dexamethasone will be given as a single oral dose of 40mg on days 1, 8, and 15 of each 28 day cycle during the induction phase of this study (Cycles 1-6 only).

Dexamethasone should be taken at approximately the same time each day. It is recommended that dexamethasone be taken in the morning to reduce insomnia. Each dose should be taken with food. If a dose of dexamethasone is vomited, the participant should continue with the regular schedule of the drug at the next dose. If a dose is missed and less than 12 hours has elapsed since the missed dose, the patient may 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 must be provided to participants to record oral administration of doses. Dose modification guidelines are described in Section 6.3.

5.2.3.1 Dose Delay or Interruption

Please refer to section 6.4 of the protocol.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Medications and supportive care

- Patients who experience worsening neuropathy from baseline should be observed for recovery, have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

- Supportive measures consistent with optimal patient care may be given throughout the study.

- Stem cell collection may be performed at the time of best response (PR, VGPR or CR or at the investigator's discretion) or after 6 cycles of therapy for those who are transplant eligible, and/or who plan to pursue transplant in the future. The standard mobilization procedures of the treating institution should be followed. Plerixafor should be the preferred mobilization agent, though cyclophosphamide or other agent may be used at the investigator's discretion. A delay of no more than 3 weeks is allowed between the end of collection and re-initiation of therapy especially if chemotherapy such as high dose cyclophosphamide was used for stem cell mobilization. Mobilization should occur as soon as possible after study treatment is stopped.
- Use of white cell growth factors (Filgrastim or acceptable equivalent) is allowed for management of treatment-induced neutropenia at physician discretion. Filgrastim or equivalent should be given according to local institutional guidelines or per the package insert. Pegfilgrastim is not to be used in place of filgrastim.

- Patients may be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.

- Patients may receive bisphosphonates per recommendations of myeloma therapy, or may follow local standard of care. A note should be placed about patients who are not receiving bisphosphonates, such as osteonecrosis of the jaw.

- If nausea and/or vomiting is/are noted at any point in time, premedication with prochlorperazine or other antiemetics may be used before future doses. Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used as needed at the discretion of the investigator.

- If nausea persists in spite of the use of standard antiemetics, additional symptom management should be initiated per institutional standard.

- Loperamide or other antidiarrheal may be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF may be given to prevent volume depletion.

- Thromboprophylaxis is recommended for all participants. Thromboprophylactic initiation and regimen choice is at the discretion of the treating physician or sites may follow the current package insert for Revlimid. It is recommended that if the platelet count falls below 30,000/mm^3, thromboprophylaxis be held to minimize the risk of bleeding and then resumed when platelet counts are equal to or above 30,000/mm^3.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

- Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals may be initiated as clinically indicated at the discretion of the treating investigator. Antivirals for other indications are also allowed.

- **The following procedures are prohibited during the study:**

    - Any antineoplastic treatment with activity against MM, other than study drugs

    - Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)

5.4 Management of Clinical Events

5.4.1 Rash

- Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted.

- Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of lenalidomide (and/or other causative agent

if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted.

- In line with clinical practice, a dermatology consult that includes a biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines).

- A rare risk is Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

5.4.2 Thrombocytopenia

- Blood counts will be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Lenalidomide administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Section 6.3). Therapy may be reinitiated at a reduced level upon recovery of platelet counts.
- A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

5.4.3 Neutropenia

- Blood counts will be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Lenalidomide administration should be modified as per dose modification recommendations in the protocol when neutropenia occurs (see Section 6.3).

5.4.4 Pregnancy

- Female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

- Female patients must meet 1 of the following:
  - Postmenopausal for at least 1 year before the screening visit
  - Surgically sterile
  - If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 120 days after the last dose of lenalidomide (Revlimid) of study drug
    - Women who are of childbearing potential, agree to practice contraception for a period of 5 months after their last dose of nivolumab
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.
    - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

- Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:
  - Practice effective barrier contraception during the entire study treatment period and through 154 days after the last dose of lenalidomide (Revlimid)
    - Men receiving nivolumab who are sexually active with women of childbearing potential must adhere to contraception for a period of 7 months after the last dose of nivolumab
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject.
    - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care.

In the absence of treatment delays due to adverse event(s), treatment may continue for 12 cycles or until one of the following criteria applies:

- Progression to overt Multiple Myeloma
- 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 Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form will be provided by the lead site. 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 number 617-632-4198.

5.6 Duration of Follow Up

Participants will be followed for **3 years** after removal from protocol therapy or until progression to active symptomatic MM or need for new therapy, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

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

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Progression to active myeloma and subsequent treatment

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

A Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form will be provided by the lead site. External sites should submit the form to the Research Project Manager.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Recommended Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Patients must meet eligibility criteria on Cycle 1 Day 1 to begin treatment. There are no pre-treatment criteria to begin a new cycle of nivolumab.

For a new cycle of treatment with lenalidomide to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/μL.
- Platelet count must be ≥ 50,000/μL.
- All other clinically significant, study drug related non hematologic toxicity must have resolved to ≤ Grade 1 or to baseline condition

If the participant fails to meet the above-cited criteria for initiation of a new cycle of treatment on day 1 of the cycle, dosing of all medications should be delayed for 1 week. At the end of that time, the participant should be re-evaluated to determine whether the above criteria have been met. If the participant continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate. The maximum delay for toxicity related to study treatment before treatment is permanently discontinued will be 3 weeks. **If a delay of > 3 weeks is clinically necessary, and the patient is showing benefit from treatment, the patient may continue on study after discussion and approval by the Principal Investigator.**

If any one of the study medications is permanently discontinued for any reason including toxicity, or FDA mandate, the patient may remain on the study at the discretion of the principal investigator.

6.2 Nivolumab

No dose reductions for Nivolumab are allowed. If Nivolumab is held on Day 1 of a new cycle, treatment with Lenalidomide/Dexamethasone will also be delayed. If Nivolumab is held during any cycle on day 15, the treating investigator should decide if lenalidomide and/or dexamethasone will be skipped using recommended guidance for retreatment below. Nivolumab may be delayed for up to 21 days or 3 weeks. A delay of up to 14 days will be allowed for participants for non-AE related events (i.e.; vacation, family emergency, etc) after discussion with the overall PI. If an alternate treatment plan for a suspected nivolumab related toxicity is proposed and is not listed in Table 11, you must first discuss and obtain approval from the Overall PI.

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 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website

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

* If any one of the study medications is permanently discontinued for any reason including toxicity, or FDA mandate, the patient may remain on the study at the discretion of the principal investigator.

Table 11 Suggested Guidelines for Nivolumab Suspected Toxicity

CTCAE 4.0 Category	CTCAE Grade	Nivolumab Action
Pneumonitis (See Section 6.2.1 for management guidelines)	**Grade 1**	Continue to treat- Do NOT OMIT
	Grade 2	Hold dose until resolved to ≤ Grade 1
	≥ Grade 3	Permanently discontinue nivolumab
Colitis (See Section 6.2.2 for management guidelines)	**Grade 1**	Continue to treat- Do NOT OMIT
	Grade 2 or Grade 3	Hold dose until resolved to ≤ Grade 1
	Grade 4	Permanently discontinue nivolumab
Increase in AST and/or ALT (See Section 6.2.3 for management guidelines)	**Grade 1**	Continue to treat- Do NOT OMIT
	Grade 2	Hold dose until resolved to ≤ Grade 1
	≥ Grade 3	Permanently discontinue nivolumab
Increase in Blood Bilirubin (See Section 6.2.3 for management guidelines)	**Grade 1**	Continue to treat- Do NOT OMIT
	Grade 2	Hold dose until resolved to ≤ Grade 1
	≥ Grade 3	Permanently discontinue nivolumab
Increase in Creatinine (See Section 6.2.4 for management guidelines)	**Grade 1**	Continue to treat- Do NOT OMIT
	Grade 2 or Grade 3	Hold dose until resolved to ≤ Grade 1
	Grade 4	Permanently discontinue nivolumab
All other related toxicities not listed previously in this table (See Section 6.2.6 for management guidelines)	**Grade 1**	Continue to treat- Do NOT OMIT
	Grade 2	Continue to treat- Do NOT OMIT
	Grade 3	Hold dose until resolved to ≤ Grade 1
	Recurrent Grade 3 or	Permanently discontinue nivolumab

	Grade 4	

If the patient discontinues nivolumab, he or she does not need to come off protocol therapy

6.2.1 Immune-Mediated Pneumonitis

Monitor patients for signs and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater pneumonitis, followed by corticosteroid taper. Permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold nivolumab until resolution for moderate (Grade 2) pneumonitis.

6.2.2 Immune-mediated colitis

Monitor patients for immune-mediated colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Withhold NIVOLUMAB for Grade 2 or 3 immune-mediated colitis. Permanently discontinue NIVOLUMAB for Grade 4 colitis or for recurrent colitis upon restarting NIVOLUMAB

6.2.3 Immune-Mediated Hepatitis

Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for Grade 2 or greater transaminase elevations, with or without concomitant elevation in total bilirubin. Withhold nivolumab for moderate (Grade 2) and permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis.

6.2.4 Immune-Mediated Nephritis and Renal Dysfunction

Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) serum creatinine elevation and permanently discontinue nivolumab. For severe (Grade 3) or moderate (Grade 2) serum creatinine elevation, withhold nivolumab and administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper; if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents and permanently discontinue nivolumab.

6.2.5 Immune-Mediated Hypothyroidism and Hyperthyroidism

Monitor thyroid function prior to and periodically during treatment. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of

hyperthyroidism. There are no recommended dose adjustments of nivolumab for hypothyroidism or hyperthyroidism.

6.2.6 Other Immune-Mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions can occur. Immune-mediated adverse reactions may occur after discontinuation of nivolumab therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, withhold nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting nivolumab after completion of corticosteroid taper based on the severity of the event

6.2.7 Immune Mediated Cardiac Toxicity

Cardiac *	M**anagement/Next Dose for Nivolumab**
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Off treatment.
*Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin **Patients with evidence of myositis without myocarditis may be treated according as "other event" Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

6.3 Lenalidomide

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 unless discussed and approved first by the overall principal

investigator. The treating investigator should determine the clinical significance of laboratory values and attribution to study medications before a treatment decision is made. All instances where lenalidomide is held, the dose will be considered missed, and will not be made up.

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 unless discussed and approved first by the overall principal investigator. 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. All instances where lenalidomide is held, the dose will be considered missed, and will not be made up.

Dose delays and modifications should be made as indicated in the following table(s) unless first discussed with the Overall PI. 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.

Table 12 Lenalidomide 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 ≥38.5º C or 101ºF	**Grade 3 or Grade 4**	Hold dose Administer Filgrastim Reduce dose one level when ANC≥1000
Thrombocytopenia	**Grade 1 or Grade 2**	Continue to treat- Do NOT OMIT and DO NOT REDUCE therapy

Aspirin prophylaxis should be held if platelets are ≤50,000	**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.

Table 13 Lenalidomide 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 Lenalidomide Including Rash related to Lenalidomide	**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
	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

If the patient discontinues lenalidomide, he or she does is not required to come off protocol therapy.

Table 14 Lenalidomide Dose Reduction

Dose Level	Lenalidomide Dose
0	25 mg
-1	20 mg
-2	15 mg
-3	10 mg
-4	5 mg

If lenalidomide is reduced for any toxicity, the dose may not be re-escalated.

6.4 Dexamethasone

Dexamethasone Dose Modifications

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 unless discussed and approved first by the Overall Principal Investigator. 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 dexamethasone has been permanently discontinued

Table 15 Dexamethasone Dose Modifications

CTCAE 4.0 Category	CTCAE Grade	Dexamethasone Dose Modification
Hyperglycemia	**Grade 1**	Continue to treat- Do NOT OMIT and DO NOT

Treat with oral medication or insulin at discretion of treating investigator		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

If the patient discontinues dexamethasone prior to maintenance, he or she is not required to come off protocol therapy.

Table 16 Dexamethasone Dose Reduction

Dose Level	Dexamethasone Dose
0	40 mg
-1	20 mg
-2	10 mg

If dexamethasone is reduced for any toxicity, the dose may not be re-escalated.

6.5 Dose Delay Guidelines

Required study schedule assessments should always correlate with the nivolumab dosing schedule. If lenalidomide and/or dexamethasone are held during a cycle, then study assessments should continue per the schedule of assessments in Section 10. If nivolumab is held at any timepoint, study calendar assessments for that day should be repeated prior to re-initiation of

nivolumab.

Table 17 Dose Delay Instructions

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

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Definitions

7.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug. **CTCAE version 4.03** will be used for this study.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

7.1.2 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- Is a **congenital anomaly/birth defect**.

- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as the *serious*, which is based on patient/event outcome or action, criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.2) and the characteristics of an observed AE (Section 7.3) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.2 Expected Toxicities

- Adverse Events List(s)

7.2.1.1 Adverse Event List of Nivolumab

Events that are listed as very common (experienced in ≥10% of patients) according to the current IB (Version 15 dated June 24 2016) include the following: diarrhea, nausea, fatigue, rash, and pruritis .

Events that are listed as common (experienced in ≥1% to <10% of patients)include: hypothyroidism, hyperthyroidism, hyperglycemia, colitis, stomatitis, mouth ulceration, vomiting, abdominal pain, constipation, dry mouth, pyrexia edema (general and peripheral), hepatitis, infusion related reactions, upper respiratory infections, increased lipase, increased amylase, increased aspartate aminotrasferase, increase alanine aminotransferase, increased blood bilirubin, hyponatremia, decreased appetite, musculoskeletal pain, arthralgias, peripheral neuropathy, headache, dizziness, nephritis, pneumonitis, dyspnea, cough, vitiligo, dry skin, erythema, alopecia, and hypertension

Events that are listed as uncommon ≥0.001% of patients to < 1% include the following: urticaria, vasculitis, rosacea, psoriasis, erythema multiforme, lung infiltration, tubulointerstitial nephritis, renal failure, acute kidney injury, encephalitis, autoimmune neuropathy, facial nerve paresis, myasthenic syndrome, demyelization, Guillain-Barre Syndrome, polymyalgia rheumatica, histiocytic necrotizing lympadenitis, bronchitis, hypersensitivity, anaphylactic reaction, duodenal ulcer, pancreatitis, uveitis, diabetes mellitus, diabetic ketoacidosis, thyroiditis, autoimmune hypophysitis, hypopituitarism, adrenal insufficiency, tachycardia, arrhythmias,

Toxic epidermal necrolysis (including Stevens Johnson Syndrome) is included as a rare risk (experienced by ≥0.00001% to <0.001% of patients).

7.2.1.2 Other Immune Mediated Adverse Events

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab should be withheld or discontinued, and corticosteroids administered accordingly. Upon improvement, nivolumab may be resumed after corticosteroid taper. If there is recurrence of any Grade 3 or 4 immune-related adverse reactions or life-threatening immune-related adverse reactions, nivolumab must be permanently discontinued. Rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab should be withheld or discontinued, and appropriate treatment instituted. For Grade 3 myocarditis, nivolumab should be permanently discontinued.

The following events have been identified during post approval use of nivolumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

- Solid organ and tissue transplant rejection has been reported in patients who have previously undergone transplantation and who were subsequently treated with programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitors, including nivolumab. Treatment with nivolumab may increase the risk of rejection in solid organ or tissue transplant recipients.

- Rapid-onset and severe GVHD, some with fatal outcome, has been reported in patients who had undergone prior allogeneic HSCT and subsequently received PD-1/PD-L1 inhibitors.

Subjects should be screened to determine whether they have undergone a prior allogeneic HSCT prior to participating in nivolumab clinical trials.

- Complications of allogeneic HSCT after treatment with PD-1/PD-L1 inhibitors including nivolumab, administered before allogeneic HSCT, may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies. Patients should be monitored closely for early evidence of transplant-related complications

7.2.1.3 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.

7.2.1.4 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.

7.3 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.

- **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.

7.4 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 to nivolumab (the study medication), all grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.5 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.

Table 18- 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

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.

There is no specific experience in the management of lenalidomide overdose in patients with MM, MDS, or MCL. In dose-ranging studies in healthy subjects, some were exposed to up to 200 mg (administered 100 mg BID) and in single-dose studies, some subjects were exposed to up to 400 mg. Pruritus, urticaria, rash, and elevated liver transaminases were the primary reported AEs. No clinically significant changes in ECGs, blood pressure, or pulse rate were observed. While no hematologic events were associated with an overdose, such events may be expected since in clinical trials; the dose-limiting toxicity was essentially hematologic. In the event of overdose, supportive care is advised.

There is no available information concerning overdose with nivolumab. Depending on the symptoms and/or signs leading to the suspicion of overdose, supportive medical management should be provided. There is no specific antidote.

7.5.1 Protocol-Specific Expedited Adverse Event Reporting Exclusions

7.5.1.1 There are no protocol specific exclusions.

7.6 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.

7.7 Expedited Reporting to Bristol-Myers Squibb (BMS)

The Overall PI, as study sponsor, will be responsible for all communications with the BMS via the MedWatch 3500A form:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm2007307.htm

With the exception of any serious adverse event that meets the FDA's criteria for expedited reporting, one should follow 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 24 hours.

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 <u>also</u> be reported in routine study data submissions.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the Nivolumab and lenalidomide administered in this study can be found in Section 7.

8.1 Nivolumab

8.1.1 Description

Nivolumab is a fully human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cell surface membrane receptor. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro.

8.1.2 Form

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) or 40 mg/4 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80, pH 6.0 and includes a 0.7 mL overfill to account for vial, needle, and syringe (VNS) holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

8.1.3 Storage and Stability

The product does not contain a preservative. Vials of nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing, and shaking.

After preparation, store the nivolumab infusion either:

- At room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- Under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.
- Do not freeze.

If a temperature excursion is noted at your site, the site must complete a temperature excursion form provided by the lead site. The lead site will then submit to Bristol- Myers Squibb to assess if the drug is appropriate for use, or should be destroyed.

8.1.4 Compatibility

Do not co-administer other drugs through the same intravenous line.
Flush the intravenous line at end of infusion.
No incompatibilities between nivolumab and polyvinyl chloride (PVC), non PVC/non DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

8.1.5 Handling

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

8.1.6 Availability

Nivolumab for injection will be supplied free of charge by BMS. The study team will provide all external sites with a study specific order form

8.1.7 Preparation

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

- Withdraw the required volume of nivolumab and transfer into an intravenous container.
- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
    - Mix diluted solution by gentle inversion. Do not shake.
    - Discard partially used vials or empty vials of nivolumab.

8.1.8 Administration

Administer the infusion over 60 minutes (+/- 10 minutes) through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Nivolumab will be administered at a flat dose of 240 mg as an intravenous infusion over 60 minutes (+/- 10 minutes) every 2 weeks (Days 1 and 15 of each 28 day cycle). The administration of nivolumab infusion must be completed within 24 hours of preparation.

8.1.9 Ordering

Each participating institution will order nivolumab directly from the supplier Bristol Myers Squibb Pharmaceuticals (BMS). A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded by the Coordinating Center. A study specific order form will be supplied by the lead site.

8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 Destruction and Return.

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible DFCI Study Monitor or designee unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification (ID) of the person disposing the containers. The method of disposal, (eg, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

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

Lenalidomide supply will be obtained through commercial supply.

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 on days 1-21 of each 28 day 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

Commercial supply of lenalidomide (Revlimid®) will be ordered through the participant's insurance and will be filled through a retail pharmacy, and shipped on a per cycle basis to the patient's home or to the treating institution's outpatient pharmacy, whichever the study team prefers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements (as listed in section 3.1.7), 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.

8.2.9 Accountability

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

8.2.10 Destruction and Return

Unused or returned supplies of lenalidomide should be destroyed and documented according to institutional policies.

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

During induction therapy, participants will receive dexamethasone as a single oral daily dose of 40mg on Days 1, 8 and 15 of cycles 1-6.

8.3.8 Ordering

Dexamethasone will be ordered from retail pharmacy through commercial drug 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

Unused or returned supplies of dexamethasone should be destroyed and documented according to institutional policies.

9. BIOMARKER, CORRELATIVE, MRD ASSESSMENT AND SPECIAL STUDIES

The mandatory correlative studies will consider several potential predictive biomarkers. As discussed in the appropriate sections of the protocol, mutations such as N-RAS, K-RAS, MYC up-regulation, and gain or loss of chromosome 1q or 1p are hypothesized to correlate with disease progression. The sample size of this phase-2 study, 41 patients, will allow exploratory analyses on TTP correlation with biomarkers. The number of biomarkers and the associated

multiplicities will only allow us to provide empirical point estimates and confidence intervals for TTP-biomarker concordance indexes.

Please refer to Appendix B for a full sample collection table. This trial will provide samples from consenting SMM patients treated with Nivolumab, lenalidomide and dexamethasone 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 several time points during the study, including before therapy, at the end of cycle 6, at the time of response determination (CR),at disease relapse, and at the time of completion 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. Samples collected for the purpose of research at Dana Farber Cancer Institute will be banked and retained for research use indefinitely.

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 immune cells will be determined.

9.1 Minimal residual disease assessment (MRD)

MRD will be assessed using Adaptive's LymphoSIGHT platform as part of normal clinical care. Bone marrow samples will be collected per the collection time described in the table of sample collection. The collection kits and shipping supplies will be provided to the sites by Adaptive Inc. These samples will be packaged whole, and shipped to Adaptive, Inc. the same day priority overnight. Using Adaptive'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. Adaptive MRD levels will be quantified using spiked-in reference sequences.

Adaptive Inc. will hold samples for up to 6 months after they have been analyzed, and then will subsequently be destroyed.

The processing of these samples will be billed to the patient's insurance, and therefore, all information requested on the online test ordering portal must be filled out completely, and not de-identified.

For Adaptive Inc. samples, use the packing supplies provided in each individual kit and follow the directions below to establish your account and order the required testing:

1. Create an online ordering profile for your physician and any staff who may order this test for your patients using the Physician Registration Form provided to you by the lead site.
    a. Enter all information under the "Ordering Physician" as the site responsible PI for the trial at your site
    b. "Online Access" should be checked off to enable online portal ordering of tests
    c. The "Designated Point of Contact" should be one non-physician member of the team as the contact for any and all study/order related questions
    d. The "Designated Point of Contact" should be the person (along with the physician) who will have access to the patient's results and be able to send them to the lead site
    e. Be sure to include your own practice as the Primary Institution
    f. Additional points of contact should list any other members of the study team who may place orders for the patients on the trial
    g. Submit the form to clinicalservices@adaptivebiotech.com to establish your site

2. Order kits for your site by placing an order to clinicalservices@adaptivebiotech.com ; ensure that you identify yourself as being part of trial 16-242; Overall PI Irene Ghobrial, MD and provide the proper shipping address for the kits

3. To order a ClonoSEQ ID test(also known as the B-Cell Clonality Test required at baseline/screening) or a Follow up Test (MRD or Tracking Test) for a patient:
    a. After logging into your account, click "New Order"
    b. Choose Ordering Physician associated with 16-242
    c. Under Trial/Study Code, enter 16-242
    d. Click Pick a Patient, and then Create New Patient (for follow up/MRD samples, select established patient- Their information will populate the form)
    e. Enter patient complete demographics (new patients only)
    f. Under Diagnosis (es)/Clinical Indication ICD Codes, Multiple Myeloma C90.00 not having achieved a remission should be selected.
    g. Under clonoSEQ Assay, choose B Cell Clonality Test (Diagnostic ID test) if it is the baseline sample. For follow up samples, select Tracking Test (Minimal Residual Disease "MRD" test)
    h. Under Billing Information, select Insurance, and enter the patient's complete insurance information (new patients only)
    i. Under patient status, select "outpatient" and enter your full institution name
    j. Enter any secondary insurance information for the patient if applicable (new patients only)
    k. Enter the patient's complete billing address (new patients only)
    l. Under Specimen Information, select " Shipping Specimen to Adaptive", Specimen Type: fresh bone marrow and the collection date

m. The unique specimen ID should be chosen by the site and able to be connected to the patient later on (you may use either letters or numbers or a combination of the two)
n. Under special instructions, please enter Fed Ex tracking number of the package
o. Print out a copy of the Test Requisition Form (TRF) and have either the Point of Contact, Additional Contacts or the Physician listed on the Physician Registration Form sign the designated signature space, and include it in the shipment
p. Retain retain a copy of the Fed Ex Waybill in the patient's research folder attached to the copy of the TRF and file in the patient's research chart
q. Please email Patrick Henrick (Phenrick@dfci.harvard.edu) and Alexandra Savell (asavell@dfci.harvard.edu) to notify of an outgoing shipment.

Diagnostic Portal Log In: **https://diagnostics.adaptivebiotech.com/account/login**

To order kits for your site: Please order via clinicalservices@adaptivebiotech.com and reference the study number, 16-242 , and include the address where the kits should be shipped

Results: The results of these tests will be sent to the lead site in the form of a PDF/scanned document emailed to the study team listed abovein real time. The patient's PHI should be redacted appropriately with only the patient's date of birth, and study specific identifier (initials and assigned study number) visible.

* External sites may choose to use an alternate method/source to bill for this test, if they so choose. This must first be discussed and approved by the lead site prior to ordering any test.

9.2 Bone Marrow Aspirate Samples

Collection of bone marrow aspirate specimens for exploratory analysis are requested at the times of all standard of care bone marrow collections. Specimens will be shipped (via traceable carrier) to and subsequently processed, analyzed, and stored at Dana-Farber Cancer Institute.

9.2.1 Specimens Requested

2 Purple Top Tubes (K2EDTA), 10mL each(3 tubes at baseline). Specimens must be collected on Mondays to Thursdays for same-day shipment. For complete sample collection table, please refer to Appendix B

9.2.2 Processing Information

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 First Priority Overnight delivery the same day the sample was collected. Please only ship Monday-Thursday. **Please see Appendix B and C for Collection Schedule and Requisition Form**

9.2.3 Shipping Information for Bone Marrow Aspirate Specimens sent to DFCI

Label all specimens with the following: Subject Initials, Subject study number (will include protocol number), Visit at which sample was drawn (screening, response, Cycle X, etc. or progression), Date sample drawn (mm/dd/yyyy), Time sample drawn (24 hour clock).

Shipping Instructions

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

1. Samples should be placed in a sealed biohazard bag and placed in a box with a fridge pack.

2. 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.

3. An electronic copy (Word or Excel) of the sample requisition form 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.

4. Please email Patrick Henrick (Patrick_Henrick@dfci.harvard.edu) and Alexandra Savell (AlexandraE_Savell@dfci.harvard.edu) to notify of an incoming shipment.

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

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

   Irene Ghobrial, MD, Dana-Farber Cancer Institute, 77 Avenue Louis Pasteur HIM Building room 240, MA551, Boston, MA 02215 Phone: (617) 582-9857 Fax: (617) 632-8535. Please retain a copy for site record maintenance. **Please see Appendix B and C for Collection Schedule and Requisition Form**

9.3 Peripheral Blood Samples

Collection of peripheral blood specimens (including serum and plasma) for exploratory analysis are requested for all patients on this trial. Purple top tube collections will be requested at the same timepoints as bone marrow samples for correlative studies (see Section 10 and Appendix B for specific time points and instructions). These specimens should be taken at the time of routine blood collection 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 indefinitely. **Please see Appendix B and C for Collection Schedule and Requisition Form**

Specimens Required: 2 x 10mL purple top tubes (K2EDTA) and 1 x 10 mL Streck tube should be collected Mondays to Thursdays for same-day shipment.

- Label all specimens with the following:
    - Subject Initials, Subject study number (will include protocol number), Visit at which sample was drawn (screening, response, Cycle X, progression etc.), Date sample drawn (mm/dd/yyyy), Time sample drawn (24 hour clock)

9.3.1 Processing Information:

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 First Priority Overnight the same day the sample was collected. Only ship Monday-Thursday.

With each shipment, please include the following:

1. Samples should be placed in a sealed biohazard bag and placed in a box with a fridge pack.

2. 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 C for Sample Requisition Form**

3. 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.

4. Please email the lead site Project Manager to notify of an incoming shipment.

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

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

   Irene Ghobrial, MD, Dana-Farber Cancer Institute, 77 Avenue Louis Pasteur HIM Building room 240, MA551, Boston, MA 02215 Phone: (617) 582-9857 Fax: (617) 632-8535. Please retain a copy for site record maintenance.

9.4 Buccal Swab Samples

9.4.1 Collection, Processing, and Shipping

1. Ideally have the patient rinse mouth out with water immediately prior to sample collection at least one hour after eating, drinking, or brushing teeth
2. Pull open the package from one end
3. Remove the swab from the tube, taking care not to touch the white swab head with your fingers
4. Insert the swab into your mouth and rub firmly against the inside of your cheek or underneath lower and upper lip. For standard DNA collection, rub for 1 minute and in all cases, for a minimum of 20 sections. Please use reasonable, firm, solid pressure
5. Slide the plastic cap over the swab handle with the flat side of the cap facing upwards and the swab facing downwards
6. Insert the swab into the clear plastic tube and push the cap into place- Next, hold the cap while pulling the swab handle outwards to release the swab material into the tube
7. Close the cap by pushing the stopper fully into the cap ensuring the stopper is flush with the cap- The tube is now completely sealed
8. Mail same day, ambient to the lead site for processing. The caps can be placed in an envelope or other container with the trial number, patient study number (if registered), date of birth, site name, collection date and time
9. Two swabs should be used for each patient to ensure adequate sample for analysis

10. STUDY CALENDAR

Screening evaluations are to be conducted within 28 days of registration. Imaging assessments that are completed within 6 weeks of registration need not be repeated at screening. If a patient had a bone marrow core biopsy done within 6 weeks of registration, a bone marrow aspirate sample need only be collected for baseline and research purposes. Baseline assessments are to be conducted on C1D1 of initial therapy and should be considered separate from screening evaluations. If screening assessments are performed within 7 days of C1D1, disease assessments (SPEP, UPEP, Immunofixation, Free light chain assay, quantitative immunoglobulins) do not need to be repeated. Lab values that are used to prove eligibility for patients with progressive (evolving) smoldering myeloma do not need to be within the 21 day window, but screening values will need to be established in window. 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 1-12 (28 days)[3]**				**Follow-Up**
Tests and procedures	**≤ 28 days prior to registration**	**≤ 21 days prior to registration**	**Day 1 of cycles 1-6[1]**	**Day 1 of cycles 7-12**	**Cycle 7 Day 1 and to confirm CR[8]**	**End of Treatment[18]**	**Every 3 Months[11]**
History and exam, height, weight. Performance Status	X		X	X		X	X
Response Assessment[17]			X	X		X	X
Toxicity Notation			X	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		X	
Free light chain assay		X	X	X		X	X
Serum and Urine Immunofixation (SPEP and UPEP) with quantitative immunoglobulins[9]		X	X	X		X	X
β2M, CRP, LDH[16]		X	X	X		X	
TSH, Free T4, Free T3		X	X	X		X	
Metastatic Bone Survey and Spine MRI OR PET/CT only[10]	X					X	
EKG[15]		X				X	
Serum pregnancy test[12]		X					
Unilateral bone marrow aspirate and biopsy[5]	X				X	X	
Research bone marrow aspirate[6]	X[5]				X[6]	X[6]	
Research Blood[7]	X[7]		X[7]	X[7]	X[7]	X[7]	
Buccal Swab[13]	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 +/- 7 days all cycles.

4- Chemistry includes sodium, potassium, chloride, bicarbonate, bun, creatinine, calcium, glucose, albumin, ALT (SGPT), total protein, AST (SGOT), total bilirubin, magnesium, and phosphorus.

5- A bone marrow biopsy is required within 6 weeks of registration. A bone marrow aspirate for clinical and research purposes is required pre-treatment and may be performed up to 28 days prior to registration. Both core and aspirate are required any time during the course of the study to confirm CR, and is also required at C7D1

6- Research bone marrow aspirate and biopsy at the same time as clinically indicated bone marrow biopsy and to confirm response.

7- Peripheral blood samples for correlative studies may be done at any time pre-treatment, though baseline and C1D1 samples should be considered separate time points.
8-If C7D1 or confirmation of response BM aspirate and core biopsy was performed within 3 weeks of either timepoint, the procedure need not be repeated. At minimum, an aspirate sample is required
9- Disease assessment/response assessment is required each Day 1 starting with C2-If the participant's disease response is not followed primarily via a UPEP (24 hour urine collection) and Urine immunofixation, these tests may be done only at screening, end of treatment, and every 3 months during treatment.
10-A CD of scans at screening and end of treatment is required to be sent to the lead site for central review. Screening scans should be sent with the eligibility packet to the lead site- This requirement includes a full body skeletal survey in addition to spinal MRI OR the patient may have only a low dose PET CT
11- Follow-up should occur every 3 months (+/- 14 days) for up to 3 years after end of treatment.
12- Women of child-bearing potential must abide by revlimid REMS procedures and may require additional pregnancy testing as described in section 3.1.7.
13- Buccal swab may be collected at any time throughout the study but should be collected pre treatment on C1D1
14- Thyroid labs are required at screening, C3D1, C6D1 and every 3 cycles thereafter, at end of treatment, and at any time that it is clinically indicated
15- Alert Overall PI immediately if there is concern for cardiac toxicity (At minimum, the following should be performed: cardiology consult, EKG, echocardiogram, and labs CPK and troponin; refer to section 6.2.7 for more details
16- B2M, CRP, and LDH are required at screening, C3D1, C6D1 and every 3 cycles thereafter, at end of treatment, and at any time that it is clinically indicated
17- A disease response assessment will be required at every Day 1 starting with Cycle 2, end of treatment, and every follow up visit (q3 months) until completion, withdrawal, disease progression, subsequent therapy or death
18- All end of treatment assessments will be performed within 14 days from the date that the decision to end treatment was made by the study team

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 (≥1 CRAB Criterion and Myeloma Defining Events ≥1 MDE):

- Increased calcium levels (corrected serum calcium >0.25 mmol/dL above the upper limit of normal or >2.75 mmol/dL) due to myeloma
- Renal insufficiency (attributable to myeloma);
- Anemia (Hb 2g/dL below the lower limit of normal or <10g/dL) due to myeloma
- Bone lesions (lytic lesions or generalized osteoporosis with compression fractures)
- Myeloma Defining Events (MDE) as follows:
    - Clonal bone marrow plasma cell percentage ≥ 60%[7]
    - An abnormal FLC-ratio ≥100 (involved kappa) or <0.01 (involved lambda)[8]
    - 2 or more focal lesions on MRI or PET-CT studies[9,10]

For measurement of response:

The disease response will be assessed using criteria based on the International Myeloma Working Group Uniform Response Criteria in Section 11.2.2.1 or FreeLite™ Disease Response Criteria in Section 11.2.2.2.

Disease response by the Modified EBMT Response Criteria in Section 11.3.2.3 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 Methods for Evaluation of Disease

All baseline evaluations should be performed on Cycle 1, Day 1 of initial therapy. Response will be assessed

every cycle for the first 6 cycles and then every 3 months in the maintenance phase. 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.

11.2.2 Response Criteria

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

11.2.2.1 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 11.1.1 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.

Response	Criteria for Response
Stringent CR (sCR)	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/l 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.
Complete Response (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.
Very Good Partial Response (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.
Partial Response (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.
Stable Disease (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.
Progressive Disease (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.

11.2.2.2 FreeLite™ Disease Response Criteria

Response	Criteria for Response
Complete Response (CR)	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 (PR)	If only measurable parameter is serum immunoglobulins free light chain (FLC), **EITHER**

	of the following changes qualify as partial response: • ≥50% decrease 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% decrease in the level of involved FLC **AND** a ≥50% decrease in the ratio of involved/uninvolved FLC from the lowest response level.
Progressive Disease (PD)	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.

11.2.2.3 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.
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.

11.2.3 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.

11.2.3.1 MRD by LymphoSIGHT (Adaptive Inc.)

MRD will be carried out according to the LymphoSIGHT™ method (Adaptive Inc, Seattle, WA) [61]. Prior studies have compared this technique to the traditional MRD immunofluorescence technique, as previously reported [62] 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[63].

11.2.4 Duration of Response and Endpoint Definitions

11.2.4.1 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.

11.2.4.2 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.

11.2.4.3 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.

11.2.5 Progression-Free Survival

The secondary 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.

11.2.6 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 DFCI Office of Data Quality 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 Data Safety Monitoring Committee According to the schedule set by the Office of Data Quality.

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 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, 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 a dropout rate of 5%, we will accrue 41 patients to the trial in order to have 39 eligible patients. The Type I and II error probabilities have been derived using exact binomial probabilities.

13.1.1 Analysis of Primary Endpoint

The primary endpoint will be the 2-year progression-free rate and will be analyzed using binomial probability and corresponding 90% confidence interval. 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.

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 with 90% exact binominal confidence interval (CI). The exact 90% CI around response rate will be no wider than 28% with 39 eligible patients

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.

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.

It is expected that approximately 20% of the patients will receive cyclophosphamide (CTX) for mobilization and this may influence the PFS. Therefore, in a secondary analysis the 2 year PFS rate will be evaluated among those patients who did not receive CTX. Assuming that among the 39 eligible patients between 5-20% of the patients receive CTX for mobilization, the treatment will be considered promising if the observed response rate is at least 62%. With this rule, there is at least 80% probability of concluding the treatment is effective, when the true rate is 70% and less than 10% if true rate is 50%.

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 41 patients will be enrolled. We expect 1.5 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

There are no stratification factors.

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. 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. No interim analysis of the outcome data is planned.

13.5 Stopping Rule for Safety

All participants will be evaluable for treatment-related toxicity from the time of therapy initiation. The serious adverse event (SAE) for this purpose is defined as any grade 4 or higher unexpected, adverse event that is assessed as being related to the study intervention.

The following table provides the probabilities of observing 3 or more SAEs after the 20th patient and before the 40th patient. For example, with 20 participants, there is 0.60 probability of observing 3 or more SAEs if a true

rate is 15% and the probability is 0.021 if a true rate is 3%.

True SAE rate	1%	3%	5%	10%	15%	20%	30%
Probability (≥SAEs)	0.001	0.021	0.075	0.32	0.60	0.79	0.96

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.

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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: SPECIMEN COLLECTION SCHEDULE

Sample Time Point	Recipient	Sample Type	Shipping Method	Container[1,2,4]
Baseline	DFCI	Peripheral Blood	Fridge pack same day	3x10mL Purple Top 1x10mL Streck Tube
		Bone Marrow Aspirate		2x10mL Purple Top
		Oragene Kit or Buccal Swab[2]	Ambient same day	2x Buccal Swabs or 1 Oragene Kit
	Adaptive	Bone Marrow Aspirate	Same day – Use kit provided	1x3ml Purple Top
Cycle 1 Day 1 (Pre Dose)	DFCI	Peripheral Blood	Fridge pack same day	2x10mL Purple Top 1x10mL Streck Tube
Cycle 2-6 Day 1 (Predose)	DFCI	Peripheral Blood	Fridge pack same day	2x10mL Purple Top 1x10mL Streck Tube
End of Cycle 6 (Cycle 7 Day 1)	DFCI	Peripheral Blood	Fridge pack same day	2x 10mL Purple Top 1x10mL Streck Tube
		Bone Marrow Aspirate		2x10mL Purple Top
Cycle 8-12 Day 1 (Predose)	DFCI	Peripheral Blood	Fridge pack same day	2x10mL Purple Top 1x10mL Streck Tube
Confirm Complete Response [3]	DFCI	Peripheral Blood	Fridge pack same day	2x 10mL Purple Top 1x10mL Streck Tube
		Bone Marrow Aspirate		2x10mL Purple Top
	Adaptive	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 1x10mL Streck Tube
		Bone Marrow Aspirate		2x10mL Purple Top
Clinically Indicated	DFCI	Bone Marrow Aspirate	Fridge pack same day	2x10mL Purple Top

[1] Purple Top= K2EDTA Tube; Streck Tube–Cell Free DNA collection tube-Please ensure you alert the lead site with enough notice if you need additional Streck tubes for your site.- All shipping materials are to be purchased and obtained by the external sites except for the buccal swabs and the Streck tubes, which will be provided by the lead site.
[2] Buccal swabs and or Oragene kits will be provided by the lead site, and can be taken/sent at any time point during the trial
[3] For definition of Complete Response, please refer to section 11.2.2
[4] Streck Tubes should be drawn before any heparinized tubes if applicable

APPENDIX C: 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 Patrick Henrick (Patrick_Henrick@dfci.harvard.edu) and Alexandra Savell (AlexandraE_Savell@dfci.harvard.edu) to alert study team of shipment and include tracking number.

Ship specimen(s) to: Irene Ghobrial, MD
Dana Farber Cancer Institute
77 Louis Pasteur Avenue
HIM 240; MA551
Boston, MA 02115

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)**	**Collection Date**	**Collection Time**
☐ Pre-treatment/Baseline	☐ Blood ☐ Aspirate ☐ Saliva	_____Streck Top _____Purple Top Buccal Swab		
☐ Cycle 1-12 Day 1 Specify Cycle_____	☐ Blood	_____Streck Top _____Purple Top		
☐ Confirm Response	☐ Blood ☐ Aspirate	_____Streck Top _____Purple Top		
☐ Cycle 7 Day 1 (end of Cycle 6)	☐ Blood ☐ Aspirate	_____Streack Top _____Purple Top		
☐ End of Treatment ☐ Disease Progression	☐ Blood ☐ Aspirate	_____Streck Top _____Purple Top		
☐ Clinically Indicated/ Standard of Care	☐ Aspirate ☐ Blood	_____Purple Top _____Streck 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.

APPENDIX D: MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, RENAL, SKIN, NEUROLOGICAL, AND PULMONARY ADVERSE EVENTS DUE TO NIVOLUMAB

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

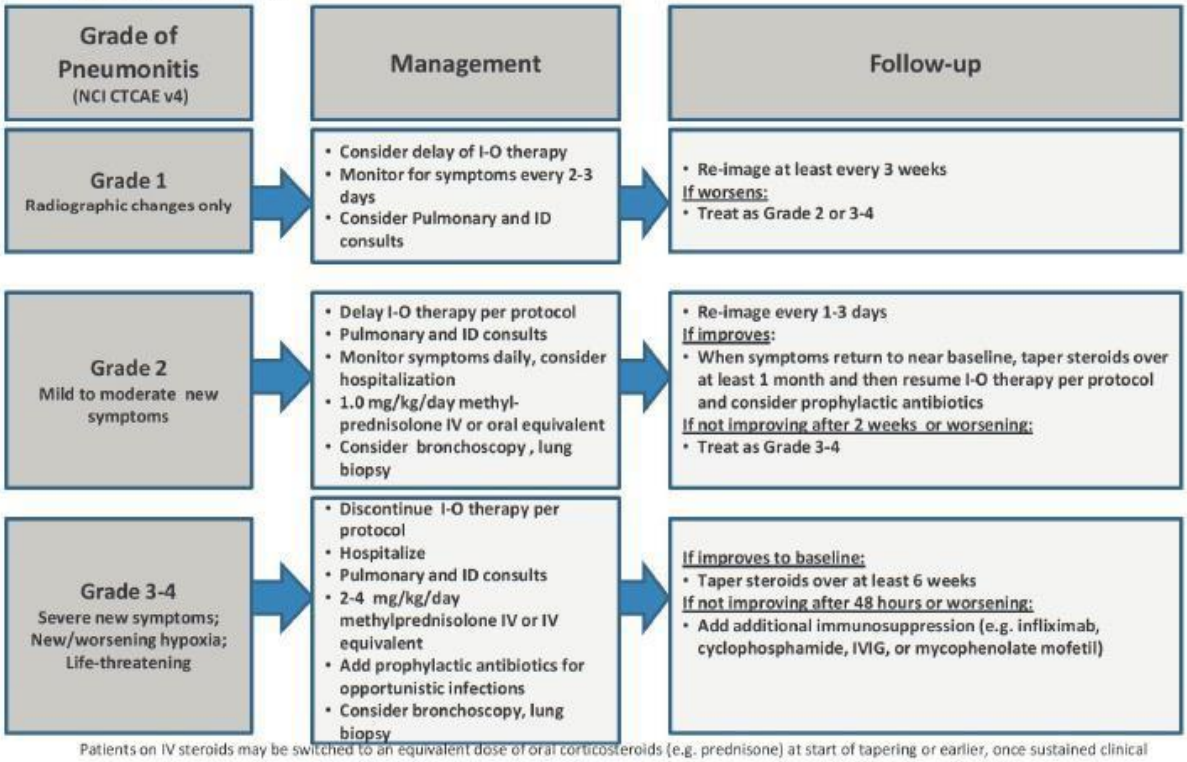
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Rash (NCI CTCAE v4)	Management	Follow-up
Grade 1-2 Covering ≤ 30% body surface area (BSA)*	• Symptomatic therapy (e.g. antihistamines, topical steroids) • Continue I-O therapy per protocol	If persists > 1-2 weeks or recurs: • Consider skin biopsy • Delay I-O therapy per protocol • Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving , taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol If worsens: • Treat as Grade 3-4
Grade 3-4 Covering >30% BSA; Life threatening consequences*	• Delay or discontinue I-O therapy per protocol • Consider skin biopsy • Dermatology consult • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent	If improves to Grade 1: • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

APPENDIX E: DANA-FARBER/HARVARD CANCER CENTER 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 serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

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 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.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

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.
- Act as the single liaison with the FDA
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

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

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- 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 and submission to the DFCI IRB, as necessary.
- 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 institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional 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 upon request.

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 for all interventional drug, biologic, or device research.

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 protocol 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

See section 4.4 of the protocol document for specific registration details and logistics.

3.7.1 Participant Registration

To register a participant, the following documents should be completed by the Participating Institution and faxed or e-mailed to the Research Project Manager at the lead site

- Copy of required laboratory tests including labs that satisfy inclusion criteria
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist complete with appropriate signatures
- Study specific cover sheet

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number.

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

Enrollment can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time unless given ample notice to the lead site.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions 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

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The lead site will provide the appropriate paperwork to submit an eligibility exception request at the time of study start up.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required 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 departure 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. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

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

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

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7 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/submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

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

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, 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.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol 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 DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

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

The DF/HCC lead site will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

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

Remote/ 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.

On-Site Monitoring

On-Site Monitoring: On-site monitoring will occur at least once per year depending on a site's accrual. 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.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports 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.

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 a formal letter regarding accrual expectations, or termination. Due to the small patient population of this trial, the accrual minimum requirement is at least one patient every year.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves 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, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, 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 Notifications

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 any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. 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, DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

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.

Protocol Number: 16-242

Principal Investigator: Irene Ghobrial, M.D.

Protocol Title: Phase II Trial of the PD-1 Antibody Nivolumab in Combination with Lenalidomide and Low Dose Dexamethasone in Patients with High-Risk Smoldering Multiple Myeloma

Instruction Sheet for Participants Regarding Reproductive Risks

Pregnancy Risk – All Patients:

You must never share lenalidomide (or other study drugs) with someone else. You must never donate blood while you are participating in this study and for at least 28 days after you have been discontinued from the study. You must receive counseling and complete phone surveys as required by the Revlimid REMS® program. Females of childbearing potential that might be caring for you should not touch the lenalidomide capsules or bottles unless they are wearing gloves. Any unused lenalidomide should be returned to the study staff.

Pregnancy Risk – Females:

If you are a female of childbearing potential, you will be required to have a negative pregnancy test prior to receiving lenalidomide.

- For the purposes of this study, 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)
  - Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

You will be required to use TWO reliable forms of birth control, one highly effective method and one additional effective method at the same time or practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) throughout lenalidomide therapy, including interruptions in therapy; and 2) for at least 28 days after discontinuation of lenalidomide. The use of birth control is required for 120 days following the last dose of nivolumab.

Pregnancy Risk – Males:

Lenalidomide is present at very low levels in human semen of healthy men for three days after stopping the drug according to a study. For some men, such as men with kidney problems, lenalidomide may be present in semen for more than three days. For these reasons, to be safe, all male patients receiving lenalidomide must use a latex condom during any sexual contact with a pregnant female or with a female of childbearing potential while you are participating in this study, including during times when lenalidomide is temporarily stopped, and for at least 28 days after permanently stopping therapy, even if you have had a successful vasectomy. You must never donate blood, sperm, or semen while you are participating in this study and for at least 28 days after you have stopped therapy. In addition, men are required to continue to use birth control for 154 days following the last dose of nivolumab.

Institutional Conflict of Interest Information Sheet

Phase II Trial of the PD-1 Antibody Nivolumab in Combination with Lenalidomide and Low Dose Dexamethasone in Patients with High-Risk Smoldering Multiple Myeloma

Protocol #16-242

You are invited to take part in a clinical trial, a type of research. For purposes of this research, you will be referred to as a "participant". This research study is studying a targeted immunotherapy as a possible treatment for this diagnosis. Bristol-Myers Squibb is supporting this research study by providing the study drug, Nivolumab. You are receiving this Information Sheet because Dana-Farber Cancer Institute has a financial interest in Nivolumab, which may be affected by the outcome of this research. This is known as a potential "institutional conflict of interest."

Nivolumab is an investigational drug, which means that the intervention is being studied and has not been approved for your type of cancer by the FDA (U.S. Food and Drug Administration). It is possible that, as the result of this clinical trial and other clinical trials involving this drug that may follow, this investigational drug could be approved by the FDA, and become widely available for sale. Specifically, the drug being investigated involves a technology that was discovered through research conducted at DFCI. As a result, a concern exists that DFCI could be biased because it stands to benefit financially from the outcome of clinical trials involving this drug.

Dana-Farber Cancer Institute ("DFCI") is committed to ensuring that all of its research and clinical activities are conducted with integrity. As part of this commitment, DFCI fully discloses the existence of all actual or potential conflicts of interest to research participants, sponsors, and regulatory bodies. Also, we have made sure that appropriate steps have been taken to ensure the safety of research participants and the reliability of research results.

First, DFCI will disclose the existence and nature of its financial interest to all research participants.

Second, DFCI will disclose the existence and nature of its financial interest to all research collaborators and in all public presentations and publications of data related to this research.

Finally, and most importantly, we want to be certain that all research participants are fully informed about the financial interest, and are able to consider this information in deciding whether to participate in this trial. To that end, if you have additional questions about DFCI's financial interests and their potential impact upon this clinical trial, or any of the steps taken by DFCI to safeguard the integrity of this research, please contact:

Roberta Driscoll, JD
Director, Office of Research Integrity
Dana-Farber Cancer Institute
450 Brookline Avenue, BP333
Boston, MA 02215-5450
617-632-4557
Roberta_Driscoll@dfci.harvard.edu

16-242: PHASE II TRIAL OF THE PD-1 ANTIBODY NIVOLUMAB IN COMBINATION WITH LENALIDOMIDE AND LOW DOSE DEXAMETHASONE IN PATIENTS WITH HIGH-RISK SMOLDERING MULTIPLE MYELOMA

PARTICIPANT SELF-ADMINISTERED DRUG DIARY

PATIENT INSTRUCTIONS:

Take your medications exactly as prescribed by your doctor. See the next page for specific doses for each medication that you are taking on this study.

- Keep capsules in the bottle(s) provided and do not transfer them to any other container. Store at room temperature.
- Lenalidomide should be taken by mouth once per day for 21 days. Capsules must be swallowed whole with water at the same time each day.
- Dexamethasone should be taken by the mouth. The days you will take dexamethasone will vary depending on your cycle. Please refer to the next page for a list of the appropriate days. Tablets must be swallowed whole and taken with food at the same time each day.
- If you vomit after taking lenalidomide or dexamethasone, do NOT take another dose. Please note any vomiting in the **Comments** section of the diary on the next page.
- If you miss a dose of lenalidomide and it has been less than 12 hours since the missed dose, take it as soon as you remember on the same day. If it has been more than 12 hours since missing a lenalidomide dose, you should not take the dose on that day, but take the next dose at the normal time on the following day.
- If you miss a dose of dexamethasone, take it as soon as you remember on the same day. If you miss taking dexamethasone for the entire day, take your regular dose the next scheduled day (**do NOT take double** your regular dose to make up for the missed dose).
- If you miss a dose please record "0" for **Number Taken** on the next page.
- If you accidentally take an extra dose of lenalidomide in one day skip the next day's dose and record the extra dose on the next page and contact your study team immediately and seek emergency medical care.
- Please bring any unused lenalidomide and all empty containers and diary to your next visit.

<table>
<tr><td colspan="3">FOR CLINIC USE ONLY:</td></tr>
<tr><td rowspan="4">• Give patient all 2 pages of Drug Diary stapled together. Provide one diary per cycle (28 days).
• Enter the appropriate dose for the current cycle.
• Complete patient identifiers and medical team contact information on page 2.
• When patient returns pill bottles and diary perform a Lenalidomide pill count and record adherence information in the box to the right.</td><td colspan="2">Staff Initials:</td></tr>
<tr><td>Date Returned:</td><td># Lenalidomide capsules returned:</td></tr>
<tr><td colspan="2"># Lenalidomide capsules that should have been taken:</td></tr>
<tr><td colspan="2">Discrepancy Notes:</td></tr>
</table>

STUDY PARTICIPANT SELF-ADMINISTERED DIARY
CYCLES 1-6

Participant Identifier: _____ Cycle #: _____

Your MD _____

Phone _____

Your RN _____

Phone _____

STUDY DRUG INSTRUCTIONS:
Take the following medications as indicated below. Record the dose of each medication on the chart to the right after taking each day.

Lenalidomide:
☐ Cycles 1-6: ___ mg by mouth on Days 1-21

Dexamethasone:
☐ Cycles 1-6: ___ mg by mouth on Days 1, 8, 15

Patient Signature:_____Date:_____

Delegated Study Staff Signature:_____Date:_____

	Date	Number Taken		Comments
		Lenalidomide	Dexamethasone	
Ex:	6/1/2009	1	1	vomited hour later
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Day 22				
Day 23				
Day 24				
Day 25				
Day 26				
Day 27				
Day 28				

STUDY PARTICIPANT SELF-ADMINISTERED DIARY CYCLES 7-12

Participant Identifier: _____ Cycle #: _____

Your MD _____

Phone _____

Your RN _____

Phone _____

STUDY DRUG INSTRUCTIONS:
Take the following medications as indicated below. Record the dose of each medication on the chart to the right after taking each day.

Lenalidomide:
☐ Cycles 7-12: ___ mg by mouth on Days 1-21

Patient Signature:_____Date:_____

Delegated Study Staff Signature:_____Date:_____

	Date	Number Taken Lenalidomide	Comments
Ex:	6/1/2009	1	vomited hour later
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			
Day 9			
Day 10			
Day 11			
Day 12			
Day 13			
Day 14			
Day 15			
Day 16			
Day 17			
Day 18			
Day 19			
Day 20			
Day 21			
Day 22			
Day 23			
Day 24			
Day 25			
Day 26			
Day 27			
Day 28			

STUDY PARTICIPANT SELF-ADMINISTERED DIARY CYCLES 7-12 FOR USE ONLY IF RECEIVING DEXAMETHASONE IN MAINTENANCE

Participant Identifier: _____ Cycle #: _____

Your MD _____

Phone _____

Your RN _____

Phone _____

STUDY DRUG INSTRUCTIONS:
Take the following medications as indicated below. Record the dose of each medication on the chart to the right after taking each day.

Lenalidomide:
☐ Cycles 7-12: ___ mg by mouth on Days 1-21

Dexamethasone:
☐ Cycles 7-12: ___ mg by mouth on Days 1, 8, 15

Patient Signature:_____Date:_____

Delegated Study Staff Signature:_____Date:_____

	Date	Number Taken		Comments
		Lenalidomide	Dexamethasone	
Ex:	6/1/2009	1	1	vomited hour later
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
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Day 26				
Day 27				
Day 28				

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**16-242**
Protocol Name:	**Phase II Trial of the PD-1 Antibody Nivolumab in Combination with Lenalidomide and Low Dose Dexamethasone in Patients with High-Risk Smoldering Multiple Myeloma**
DFCI Site PI:	Irene Ghobrial, MD
DFCI Research Nurse:	Kaitlen Reyes, DNP; John Harran, Eileen Regan Laura Amweg, Kathleen Colson, Kristen Cummings, Heidi DiPietro, Meghan Leahy Ray

Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.
Please also refer to ONC 15: Oncology Nursing Protocol Education Policy
***** Remember to check the ALERT PAGE*****

SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL

Study Design	**Nivolumab** is a fully human monoclonal antibody that targets the PD-1 cell surface membrane receptor. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro. **Lenalidomide** (REVLIMID) is a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. **Dexamethasone** is a synthetic adrenocortical steroid. • The Study Design is in Section 1.1 • The Study Rationale is in Section 2.9 • A cycle is defined as 28 days in Section 5.1
Dose Calc.	• **Nivolumab** is dosed in fixed dosing, 240 mg IV • **Lenalidomide** is dosed in fixed dosing, between 5-25 mg (increments of 5 mg for dose reductions) • **Dexamethasone** is dosed in fixed dosing, 40 mg or 20 mg or 10 mg for dose reductions
Study Drug Administration	Agent *Administration* Guidelines are found in Section 5.2 • **Nivolumab** is given IV every other week on Days 1&15; **Lenalidomide** is PO Days 1-21; **Dexamethasone** is PO Days 1, 8, 15 for Cycles 1-6 ONLY • **Nivolumab** is given IV over 60 minutes (+/- 10 minutes); No standard premeds required, unless history of infusion reaction. A 60 min post-infusion observation period is **suggested**, especially during first 2 cycles, but **not mandatory** per protocol. • The drugs may be administered in any order. • Criteria to treat DAY 1: ANC≥1,000; PLT≥50; Other drug related, non-heme tox ≤Grade 1 or baseline. • Criteria to treat DAY 15: For Lenalidomide: ANC≥1,000; PLT≥30; Hgb≥8 Other drug related less than Grade 3 or baseline. For Nivolumab: AST≤90; ALT≤156; Bilirubin≤1.8; Creatinine≤1.95 or ≤1.5 x baseline • Fasting is not required. • Lenalidomide capsules and Dexamethasone tablets should be swallowed whole, and should not be broken, chewed or opened. Administration should be at approximately the same time each day. If a dose is missed and less than 12 hours has elapsed since the missed dose, the patient may 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.
Dose Mods & Toxicity	*Dose Modifications/Dosing Delay for Toxicity* are outlined in Section • This protocol uses NCI CTCAE criteria, version 4.03 • There are no dose modifications for Nivolumab, there are dose reductions per protocol for Lenalidomide and Dexamethasone.
Con Meds	*Concomitant Therapy* Guidelines are in Section 5.3.1 • Stem cell mobilization and collection may be performed at time of best response or after 6 cycles of therapy. • Filgrastim is allowed, pegfilgrastim is NOT. • Transfusions and supportive care are allowed; bisphosphonate therapy included.
Required Data	*Study Calendar and Assessment Required data* are outlined in Section 10 • The study calendar is in Section 10 • **Vital signs:** Before any infusion. • **ECGs**: One at screening and one at EOT. • **NO PK's or biomarkers.**

Charting Tips	**All study drugs require documentation of exact administration time.** Please be sure to DOCUMENT study medication **actual** UP/DOWN times in medical record (e.g. LMR, eMAR, nursing notes). **Edit eMAR as needed to match the exact time given**. • If there is a discrepancy in the infusion time, delay in administration, or the infusion takes longer than is permitted by the guidelines of the protocol, please **document the reason for the discrepancy in the medical record.** Please be sure to also DOCUMENT any required observation periods, any additional vital signs, routes of administration, injection sites, etc.

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November XX, 2017

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Re: 16-242 A Phase II Trial of the PD-1 Antibody Nivolumab in Combination with Lenalidomide and Low Dose Dexamethasone in Patients with High-Risk Smoldering Multiple Myeloma

ClinicalTrials.gov Identifier: NCT02903381

Dear XXXXXXXX,

We are reaching out to you to follow up on the recent closure of the clinical trial by the Food and Drug Administration that you had been enrolled on.

On August 31st, 2017, the FDA requested that the company that makes this drug (Bristol-Myers Squibb) notify patients of safety concerns that were seen on two clinical trials using the drugs pembrolizumab (a similar drug to nivolumab), revlimid and dexamethasone.

It was reported that there was an increased risk of death on those trials. This risk may also be associated with nivolumab. Although nivolumab is not the same drug, it works in a similar way and these findings may be relevant to your safety.

We are formally requesting that you contact us immediately if you experience any new side effects. If you never received nivolumab, revlimid, or dexamethasone on this clinical trial, please retain this letter for reference.

Please contact me at (617) 632-4198 or at Irene_Ghobrial@DFCI.HARVARD.EDU if you have any questions regarding the clinical hold, the future of the trial, or your safety as it relates to these findings.

Sincerely,

_____

Irene M. Ghobrial, MD
Sponsor-Investigator