Local Protocol #:17-212
Janssen Protocol #: [redacted]

TITLE: D-PRISM (Precision Intervention Smoldering Myeloma) **A Phase II Study of the CD38 Antibody Daratumumab in Patients with High-Risk MGUS and Low-Risk Smoldering Multiple Myeloma**

Coordinating Center: Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02115
[redacted]

Principal Investigator (PI): Irene M. Ghobrial, MD
Dana-Farber Cancer Institute
[redacted]

Statistician:
Lorenzo Trippa, PhD
Dana-Farber Cancer Institute
[redacted]

Project Manager:
Alexandra Savell
Dana-Farber Cancer Institute
[redacted]

Agent(s): Daratumumab, Supported by Janssen

IND #: 134, 093
IND Holder: Irene Ghobrial, MD

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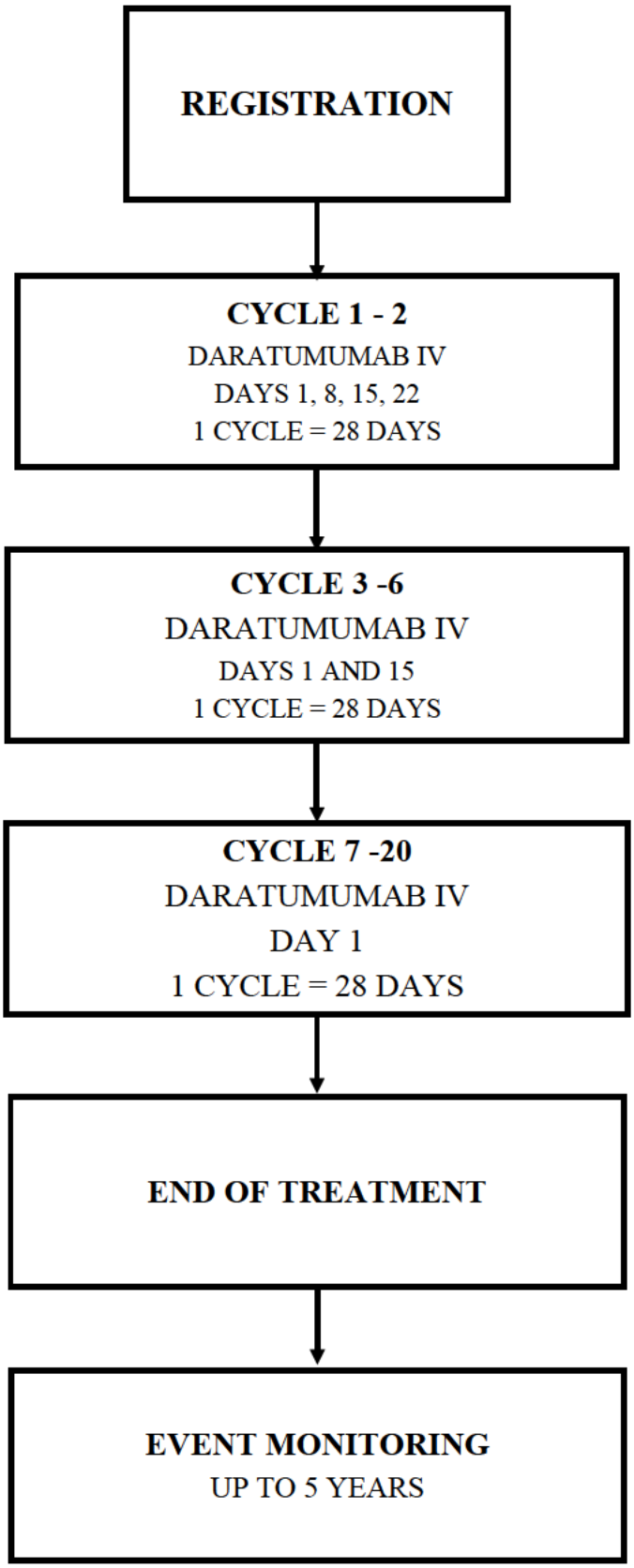
SCHEMA


REGISTRATION
CYCLE 1 - 2
DARATUMUMAB IV
DAYS 1, 8, 15, 22
1 CYCLE = 28 DAYS
CYCLE 3 -6
DARATUMUMAB IV
DAYS 1 AND 15
1 CYCLE = 28 DAYS
CYCLE 7 -20
DARATUMUMAB IV
DAY 1
1 CYCLE = 28 DAYS
END OF TREATMENT
EVENT MONITORING
UP TO 5 YEARS

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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

Abbreviation	Term
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system
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

Abbreviation	Term
Hb	Hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
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

Abbreviation	Term
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
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

1. OBJECTIVES

The concept of initiating therapy after end organ damage is analogous to initiating therapy after the development of metastatic cancer in solid tumors. Indeed, the concepts of screening, early detection and intervention are part of the major curative advances that have been achieved in solid tumors while metastatic cancer remains incurable in these same cancers. It is, therefore, not surprising that Multiple Myeloma remains incurable, in spite of all the advances in therapeutic interventions. Could it be because we are waiting too long – until metastatic myeloma occurs – to treat our patients? In such a condition, watchful waiting may actually be more harmful to the patient than early intervention.

The paradigm of therapy in Smoldering Multiple Myeloma (SMM) is changing as we develop better therapeutic agents that prevent end organ damage and improve survival of patients with Multiple Myeloma (MM)[1-4]. 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[5]. 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 current understanding is that transformation of MGUS/SMM to MM is likely due to a clonal evolution and clonal competition/selection that is Darwinian-like[6,7] leading to expansion of "winner clones" that have a more proliferative advantage leading to disease progression[8,9]. Most studies defining this model in MM have been performed using samples of patients with MM or relapsed MM[10,11,12].

However, even in patients with high-risk smoldering myeloma, there is significant clonal heterogeneity that may indicate that cure may not be achievable at this stage of the disease.

An important step in the progression of tumors is evasion and suppression of the host immune system. There is an active immune response during the early stages of tumor growth in MGUS, which controls the growth but does not fully eliminate the tumor clone. As tumor growth progresses to the stages of SMM and active MM, there is an associated cellular and humoral immune deficiencies[13], indicating that the evolution of disease in MM is associated with an immunosuppressive milieu that fosters immune escape.

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[14]. The term SMM was first described by Greipp and Kyle et al in 1980[15] and was followed by many other descriptions terming it indolent MM[16], or Durie Salmon Stage I[17]. 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/dL and/or ≥10% monoclonal plasma cells in the bone marrow (BM), Table 1[18,19]. 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[14].

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% [20]; an abnormal FLC-ratio ≥100 (involved kappa) or <0.01 (involved lambda) [21]: and/or 2 or more focal bone marrow lesions detected by functional imaging including PET-CT and/or MRI [22,23]. 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[24]. The most common factors used to stratify patients with SMM are the Mayo Clinic criteria[24,25] and the Spanish PETHEMA criteria[26]. 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)[24,25], 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[24,25]. 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[26].

The paradigm of therapy in Smoldering Multiple Myeloma (SMM) is changing as we develop better therapeutic agents that prevent end organ damage and improve survival of patients with multiple myeloma (MM)[1-3]. Indeed, recent studies of a phase III trial of lenalidomide and dexamethasone versus placebo showed improved response, progression free survival and overall survival in patients with high risk smoldering MM compared to placebo control[5].

Therefore, we hypothesize that a long therapeutic intervention with Daratumumab at the stage of high-risk MGUS and low-risk smoldering myeloma will lead to a complete eradication of the tumor clone and potential cure in a subset of these patients.

We will test this hypothesis by first examining the depth of response in these patients (primary objective) and by defining the number of patients in MRD negative disease during follow up every 6 months for up to 5 years (secondary objective).

1.1 Overview of Study Design

This is a single-arm, phase II study using single agent daratumumab in patients with high-risk MGUS and low-risk smoldering multiple myeloma.

1.2 Number of Patients

A total of 50 eligible patients will be included on this study. Enrollment includes patients who receive the first day of therapy. Patients who are registered, but never start protocol therapy should be replaced.

1.3 Duration of Study

A treatment cycle is defined as 4 weeks in length. During Cycles 1 and 2, patients will receive daratumumab weekly. During cycles 3 through 6, daratumumab will be administered every 2 weeks. During cycles 7 through 20, daratumumab will be administered every 4 weeks.

For information regarding dosing of daratumumab, please reference section 5.1. For information regarding dose modifications of daratumumab, please refer to section 6.0.

There is no maintenance therapy. Patients will be followed for up to five years after discontinuation of therapy.

1.4 Primary Objectives

- To determine the proportion of patients who are in VGPR or better after twenty cycles of therapy with Daratumumab. This will be determined at the time of best overall response.

1.5 Secondary Objectives

- To determine the number of patients, with VGPR or better, who are MRD negative disease at the completion of therapy and every 6 months after therapy for up to 5 years.
- To assess duration of response.
- To assess safety of the agent in this patient population.
- To evaluate clonal heterogeneity in these patients using deep sequencing at the DNA and RNA level and determine association of genomic aberrations with response/progression to daratumumab and progression to SMM/MM.
- To evaluate T cell response (flow cytometry, TCR sequencing, functional T cell status) in this patient population.
- To assess changes in the immune microenvironment in high-risk MGUS and low-risk SMM patients over the course of the study; to assess these immune changes and association with progression to SMM or MM.
- To examine the immunoglobulin sequence in MGUS and SMM patients to determine if common clonal sequences are noted among high-risk MGUS and low-risk SMM, and to evaluate whether common Ig sequences are associated with progression.

- To assess the rate of secondary hematologic malignancies

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 [31]. In 2010 the International Myeloma Working Group (IMWG) defined monoclonal gammopathy of undetermined significance (MGUS) by the presence of serum M-protein < 3 g/dL, clonal plasma cell population in the bone marrow < 10%, and the absence of end-organ damage such as hypercalcemia (serum calcium ≥ 11 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 [32]. Smoldering multiple myeloma was defined by the presence of serum M-protein ≥ 3 g/dL or urinary monoclonal protein ≥500 mg/dL and/or clonal bone marrow plasma cells 10-60% 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 [33]. 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%) [34]. 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 [24,25]. 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 [20].

Table 1: Definitions currently available for MGUS and smoldering myeloma

International Myeloma Working Group criteria, 2010 version[32]	
MGUS	▪ Serum M protein <3 g/dL ▪ Clonal bone marrow plasma cells <10% ▪ Absence of myeloma defining events and amyloidosis
SMM	▪ Serum M protein ≥3 g/dL ▪ and/or clonal bone marrow plasma cells 10% - 60% ▪ or urinary monoclonal protein ≥500 mg per 24 hours ▪ or FLC ratio < 0.125 or > 8 ▪ or ≥ 95% abnormal plasma cells in the bone marrow ▪ or immunoparesis of one or more immunoglobulins ▪ Absence of myeloma defining events and amyloidosis
MM	▪ Clonal bone marrow plasma cells ≥10% and/or biopsy proven plasmacytoma ▪ Presence of serum and/or urinary monoclonal protein at any level ▪ Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder (CRAB criteria) o Hypercalcemia: Serum calcium >0.25 mmol/L above upper limit of normal or > 2.75 mmol/L (> 1 mg/dL above upper limit of normal) o Renal insufficiency: Serum creatinine > 173 µmol/L (>2 mg/dL) o Anemia: Normochromic, normocytic with a hemoglobin value of >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL o Bone lesions: Lytic lesions, or osteoporosis with compression fractures ▪ Or any **MYELOMA DEFINING EVENTS (MDE)** as follows: o Clonal bone marrow plasma cell percentage*> 60%[20] o An abnormal FLC-ratio ≥100 (involved kappa) or <0.01 (involved lambda)[21]>1 or more focal lesions on MRI or PET-CT studies(≥[22, 23]

2.2 Risks of progression in MGUS

The Mayo Clinic criteria are primarily based on the levels of serum protein markers (serum protein electrophoresis [SPEP] with immunofixation and FLC assay). In a retrospective study of 1148 patients diagnosed with MGUS with long-term follow-up, M-protein > 1.5 g/dL, non-IgM MGUS, and a sFLC ratio < 0.26 or > 1.65 were independent risk factors for progression. At 20 years, patients with no risk factors had a 5% risk of progression compared with 21%, 37%, and 58% for patients with 1, 2, or 3 risk factors, respectively[71].

In contrast, the risk stratification scheme of the PETHEMA Study Group has focused on the use of multiparameter flow cytometry of the BM to quantify the ratio of abnormal, neoplastic plasma cells (aPCs) to normal plasma cells. At 5 years of follow-up, patients with MGUS with neither ≥ 95% aPCs nor DNA aneuploidy were found to have a very small, 2% risk of progression compared with a 10% risk for patients with one risk factor and a comparatively high 46% risk of progression at 5 years for patients with both[72].

Table 2: Risk stratification of smoldering MM criteria is defined below:

Model	Risk Factors	No. of Risk Factors	5-year progression %	Relative Risk
Mayo Clinic Model	- M-protein ≥ 3 g/dL - ≥ 10% BM plasma cells - FLC ratio < 0.125 or > 8	1	25	1
		2	51	2.0
		3	76	3.0
		Total	51	NA
Spanish (PETHEMA) Model	- ≥ 95% aPC - Immunoparesis	0	4	1
		1	46	11.5
		2	72	18
		Total	46	NA

2.3 MGUS and SMM consistently precede 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[35]. 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 [36].

2.4 Molecular studies in MGUS and SMM

A recent study using SNP-based arrays compared MGUS, SMM and MM samples [37]. 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 3: 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 post-transcriptionally and are being implicated in a large number of cancers [38]. 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 [39]. 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 [38,39]. The mir17 cluster has been shown to upregulated by the transcription factor c-Myc, which is considered a late event in myeloma progression[40-42].

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[10]. 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[11,12,43-45]. 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[37,46,47].

2.5 Definition of SMM and MM

The diagnosis of smoldering (asymptomatic) multiple myeloma (SMM) is based on [48,49]:

- Serum monoclonal protein (IgG 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 >.275 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 [48,49]

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 ≥100, 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 >1 focal lesion that is at least 5 mm or greater in size

2.6 Daratumumab

Daratumumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, in a variety of hematological malignancies including MM, leukemia, and non-Hodgkin's lymphoma (NHL).

Daratumumab induces lysis of CD38-expressing tumor cells, by a wide spectrum of mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP), through activation of complement proteins, natural killer (NK) cells, and macrophages, respectively [de Weers 2011, Overdijk 2013]1,19.JNJ-54767414 Daratumumab Clinical Protocol 54767414SMM2001 Amendment 1 22 Approved, Date: 20 January 2015

For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding daratumumab, refer to the Daratumumab package insert [Daratumumab USPI].

2.6.1 Nonclinical Studies

Preliminary pharmacodynamic studies suggest that daratumumab utilizes multiple effector cell functions, resulting in immune mediated killing of CD38-expressing tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary CD38-expressing MM cells, complement-dependent cytotoxicity (CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody-mediated activation of the complement proteins [73]. Daratumumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC) is slower in its action, with maximal ADCC by daratumumab observed at 4 hours in vitro [73]. Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro[74]. Further, in vitro studies indicated that daratumumab inhibited the cyclase activity of CD38 and stimulated the CD38 hydrolase activity (Study No. GMB 3003-013).

Studies on proliferation of and release of cytokines in human blood cells have indicated that daratumumab does not exert target-specific agonistic activity. The cytokine release observed is mainly caused by the Fc-portion of IgG1 and comparable to that of approved therapeutic antibodies already in clinical use. Specific binding of daratumumab was detected in multiple tissues of both human and chimpanzee origin.

2.6.2 Toxicology

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. The primary toxicities identified in chimpanzees were infusion-related reactions during the first, but not subsequent, daratumumab infusions and thrombocytopenia. Anemia was observed in cynomolgus monkeys. The binding affinity of daratumumab is significantly higher for chimpanzee platelets than for human platelets, suggesting that thrombocytopenia may be less pronounced in humans. The effect on platelets and red blood cells (RBCs) was reversible.

Depletion of specific lymphocyte phenotypic cell populations, as expected, based on the intended pharmacological effect of daratumumab, was observed in both chimpanzees and cynomolgus monkeys. No genotoxicity, chronic toxicity, carcinogenicity, or reproductive toxicity testing has been conducted.

2.6.3 Clinical Studies

Preliminary data as of 31 July 2014 from 5 ongoing clinical studies are summarized. For further details and the most up-to-date information, please refer to the Daratumumab IB.
As of June 30, 2016, about 3,147 patients have been enrolled in studies using daratumumab via intravenous infusions. 717 patients received daratumumab alone and approximately 1310 received daratumumab in combination with other drugs used to treat multiple myeloma

(lenalidomide, bortezomib, pomalidomide, carfilzomib, dexamethasone, melphalan, prednisone, thalidomide)

2.6.4 Clinical Pharmacokinetics

Pharmacokinetic (PK) data are available from Study GEN501 Part 1. The doses ranged from 0.005 to 24 mg/kg. The PK profile was consistent with target mediated disposition (TMD) with rapid target-related clearance at low doses and slower clearance at higher doses. Following long-term treatment, clearance may decrease as the tumor burden decreases. The preliminary PK data in Studies GEN501 Part 2 and MMY2002 are consistent with the PK profile obtained in GEN501 Part 1. Preliminary PK data from Study GEN503 show that following both the first dose and multiple repeated doses, the PK profile of daratumumab in combination with lenalidomide and dexamethasone is similar to what was observed in Study GEN501 following the same dose and schedule. The data suggest that lenalidomide and dexamethasone do not affect the PK profile of daratumumab.

2.6.5 Preliminary Efficacy

Preliminary efficacy data for Study GEN501 Parts 1 and 2 were presented at the 2013 and 2014 American Society of Clinical Oncology (ASCO) Annual Meetings, respectively. As the study is still ongoing, and data reconciliation activities are underway, the data should be considered preliminary. Among 12 subjects treated with daratumumab in Part 1 at doses ≥ 4mg/kg, 5 partial responses (PRs) and 3 minimal responses (MRs) were observed. Seven (7) of these subjects had a 50 to 100% concomitant reduction in bone marrow plasma cells. Among 29 subjects treated with 8 mg/kg daratumumab in Part 2, 3 subjects (10%) had a PR; the response rate was 10%. Among 20 subjects treated with 16 mg/kg, 2 subjects (10%) had a CR, 1 subject (5%) had a very good partial response (VGPR), and 4 subjects (20%) had a PR; the response rate was 35%.

2.6.6 Safety and Tolerability

In general, daratumumab is tolerated well. Maximum tolerated dose (MTD) has not been reached following intravenous (IV) infusions up to 24 mg/kg monotherapy and 16 mg/kg in combination studies. The most frequently reported adverse events (AEs) across the daratumumab program have been infusion-related reactions (IRRs) following single agent therapy. Among all subjects treated in ongoing studies (monotherapy and combination therapy), IRRs have been reported in 49% of subjects; among 151 subjects treated with 16 mg/kg daratumumab monotherapy in Studies GEN501 and MMY2002, the percentage of subjects with a reported IRR was identical (49%) to what was observed across all treated subjects. The most frequently reported adverse reactions (incidence ≥20%) were: infusion reactions, neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, muscle spasms, back pain, pyrexia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy and upper respiratory tract infection. Among subjects treated with 16 mg/kg daratumumab monotherapy, the most commonly reported IRRs were nasal congestion (8%), cough (7%), and rhinitis allergic and throat irritation (5% each). Grade 3 or higher IRRs were reported in 5% of subjects treated with 16 mg/kg daratumumab as monotherapy, with bronchospasm and hypertension being the most frequently reported Grade 3 or higher IRRs (1% each).

Across all ongoing studies, bronchospasm was reported in 10 subjects. Early in daratumumab development, in Study GEN501, 2 cases of bronchospasm were reported 24-48 hours following the second full-dose infusion of daratumumab. With the exception of those 2 cases, which had a delayed onset, all other reported bronchospasm events occurred following the first dose. All of the events occurring during the infusion period resolved quickly after standard treatments were administered. The daratumumab infusion was restarted, and no new onset of bronchospasm occurred. Most of the subjects who experienced bronchospasm had underlying respiratory diseases (asthma, chronic obstructive pulmonary disease [COPD], and others).

Among the 151 subjects treated with 16 mg/kg daratumumab as monotherapy in Studies GEN501 and MMY2002, the most frequently reported AEs (reported in >10% of subjects) were fatigue (29%); anemia (23%); nausea (19%); back pain (18%); cough (17%); thrombocytopenia (16%); decreased appetite (13%); pyrexia, dyspnea, upper respiratory tract infection (12% each); nasal congestion and neutropenia (11% each). Grade 3 and higher AEs were reported in 48% of subjects treated with 16 mg/kg monotherapy daratumumab. The most frequently reported Grade 3 or higher AEs were anemia (13%) and thrombocytopenia (9%). All other Grade 3 and higher AEs were reported in <5% of subjects. No deaths due to daratumumab-related AEs have been reported in any ongoing study.

In a single center safety study of accelerated daratumumab in patients receiving standard of care daratumumab therapy, twenty-eight patients were treated with daratumumab utilizing the accelerated rate, 8 of which received the accelerated infusion with their third dose of daratumumab[76]. The premedication regimen varied patient-to-patient and did not impact tolerability of the accelerated infusion. There were 5 patients who did not receive any steroid premedication and 3 who received reduced doses (< 12 mg) of dexamethasone. Of the 28 patients treated, there was only 1 adverse reaction - a grade 2 hypertension during which the infusion was paused for a patient that had received 10 prior infusions at standard rates. The patient received a diuretic, the infusion was resumed and subsequently increased to the accelerated rate without further incidence of hypertension. There were no grade 3 or higher IRRs. At the 4-week follow-up, all patients remaining on daratumumab treatment continued at the accelerated infusion rate. Please refer to **Appendix F** for further details regarding the rapid infusion guidelines.

2.7 Trial Rationale

Daratumumab is a targeted immunotherapy that binds to tumor cells that overexpress CD38, a transmembrane glycoprotein. Plasma cells in patients with SMM express high levels of CD38, similar to plasma cells in symptomatic MM [51]. Daratumumab, as a single agent, has shown clinical activity at 16 mg/kg in patients with relapsed/refractory MM who have already failed a number of prior therapies and whose myeloma clones have become resistant to many therapies. Daratumumab has also demonstrated an acceptable and manageable safety profile.

Patients with MGUS and SMM are asymptomatic and relatively immunocompetent. In current practice, the standard of care for subjects with MGUS and SMM is watchful waiting. For high-risk patients, treatment under clinical trials has been recommended[52].

As an immunotherapy, daratumumab's immediate and effective cell-mediated (and potentially direct) cytotoxic effects against MM cells may be an ideal mechanism for providing disease interception and early intervention at the MGUS and SMM stage. Furthermore, the low risk of serious side effects increases the appeal of daratumumab as a treatment option to prevent and/or delay transition to symptomatic MM.

Therefore, this study is designed to examine the depth of response (primary objective) and by defining the number of patients in MRD negative disease during follow up every 6 months for up to 5 years (secondary objective) using a long therapeutic intervention with Daratumumab at the stage of high-risk MGUS and low-risk smoldering myeloma. This may lead to a complete eradication of the tumor clone and potential cure in a subset of these patients.

2.8 Correlative Studies Background

2.8.1 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[6,7]. The genomic complexity in MM was recently corroborated by massive parallel-sequencing studies displaying the lack of a universal driving mutation[10]. Recent studies have shown intraclonal heterogeneity that occurs at different stages of progression in MM[11,12]. 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[8,9]. Point mutations such as N-RAS, K-RAS, MYC up-regulation[53], and gain or loss of chromosome 1q or 1p seem to correlate with disease progression from MGUS and SMM[42]. A progressive increase in the incidence of copy number abnormalities from MGUS to SMM and to MM has been recently observed[54].

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)[10,12]. 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[55]. Germline DNA will also be obtained from a buccal swab from all patients. De-identified specimens or genetic data may be placed into one or more publicly-accessible scientific databases such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP).

2.8.2 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[10,56]. Briefly, somatic single nucleotide variants are determined using the MuTect algorithm[57]. 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[58]. 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[59], and open vs. closed chromatin status[60]. Focal, as well as arm-level, copy number variations will be determined based on whole exome sequencing and subsequent application of the GISTIC algorithm[61].

2.8.3 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[62,63-65]. 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[63-65].

2.8.4 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[66,67]. 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.

2.8.5 T cell specific responses

Previous daratumumab clinical studies in myeloma have demonstrated robust T cell changes in the daratumumab treated patients, with significant CD8+ T cell expansion that was higher in responding patients compared to non-responders. In addition, naïve CD8+ T cells decreased, and central memory CD8+ T cells increased. T cell clonality was monitored by TCR sequencing (Immunoseq^{TM}) and significantly increased with daratumumab treatment. Responders had significantly higher changes in clonality compared to non-responders. In addition, CD38+ immune suppressive cells (regulatory T cells, MDSC) were noted to decrease with daratumumab treatment. This data suggests that daratumumab may increase the adaptive immune response against malignant disease, and in patients with pre-malignancy who are treatment naïve, this immune response could be even more robust. Therefore, we will examine the T cell response to daratumumab treatment in this study through in depth immunophenotyping (flow or CyTOF), functional studies examining T cell response pre- and post-daratumumab treatment.

2.8.6 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 in Appendix B. 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.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Age ≥ 18 years

3.1.2 Must meet criteria for high-risk MGUS or low-risk smoldering myeloma as described below:

High-Risk MGUS

<u>Must have <10% plasma cells and <3.0g/dL M-spike and at least 2 of the following 3 criteria:</u>

1. Abnormal free light-chain (FLC) ratio (<0.26 or >1.65)
2. M-protein concentration (≥1.5 g/dL)
3. Non-IgG M protein (including IgA)

Low-Risk Smoldering Multiple Myeloma

<u>Must only present with 1 of the following criterion:</u>

1. Monoclonal Protein ≥ 3 g/dL
2. ≥ 10% Bone Marrow Plasma Cells
3. FLC ratio < 0.125 or > 8

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

- Increased calcium levels (corrected serum calcium >0.25 mmol/dL above the upper limit of normal or >0.275 mmol/dL)
- Renal insufficiency (attributable to myeloma)
- Anemia (Hb 2 g/dL below the lower limit of normal or <10 g/dL)
- Bone lesions (lytic lesions or generalized osteoporosis with compression fractures)
- No evidence of the following new criteria for active MM including the following: Bone marrow plasma cells >60%, Serum involved/uninvolved FLC ratio ≥100, and MRI with more than one focal lesion

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

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

3.1.5 The following laboratory values obtained ≤ 42 days prior to registration:

- ANC ≥ 1000/µL
- PLT ≥ 50,000/µL
- Total bilirubin ≤ 2.0 mg/dL (If total is elevated check direct and if normal patient is eligible.)
- AST ≤ 3 x institutional upper limit of normal (ULN)
- ALT ≤ 3 x institutional upper limit of normal (ULN)
- Creatinine ≤ 2 mg/dL or Creatinine Clearance ≥ 40 mL/min

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

3.1.7 Female patients who are postmenopausal for at least 1 year before the screening visit or are surgically sterile are eligible. Females of childbearing potential (as defined below) may also be eligible but must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 42 days of registration.

- 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)

3.2 Exclusion Criteria

3.2.1 Any prior therapy for symptomatic Multiple Myeloma or smoldering Multiple Myeloma should also be excluded, including prior use of IMIDs, proteasome inhibitors, or CD138 inhibitors. Prior therapy for smoldering Multiple Myeloma with agents that are not therapeutically active against MM is not an exclusion criterion. Other prior treatment may be allowed after discussion and approval by the overall PI.

3.2.2 Other concurrent chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered investigational. Prior therapy with bisphosphonates is allowed. Prior radiation therapy to a solitary plasmacytoma is allowed.

3.2.3 Concurrent exposure to any commercially available agents known to be active against SMM and MM.

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

3.2.5 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.

3.2.6 Subject has known chronic obstructive pulmonary disease (COPD) or severe, persistent asthma with a Forced Expiratory Volume in 1 second (FEV1) < 50% of predicted normal.

- Note that FEV1 testing is required at screening for patients suspected of having COPD or severe, persistent asthma and subjects must be excluded if FEV1 <50% of predicted normal.

3.2.7 Subject has known moderate or severe persistent asthma within the past 2 years or currently has uncontrolled asthma of any classification.

- Subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study

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

3.2.9 Pregnant or nursing women will be excluded from the study.

3.2.10 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Daratumumab.

3.2.11 Seropositive for or has active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) as defined by a positive test for hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).

- Subjects with resolved infection (ie, subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

- Those who are seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

3.2.12 Major surgery within 4 weeks before enrollment.

3.2.13 Subject is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

3.2.14 Vaccination with live attenuated vaccines within 4 weeks of first study agent administration

3.2.15 Subject has clinically significant cardiac disease, including significant ischemic

coronary disease, congestive heart failure (New York Heart Association [NYHA] Class III or IV), unstable arrhythmias, myocardial infarction or unstable angina within 6 months before randomization, a history of additional risk factors for torsades de pointes (eg, electrolyte abnormalities, family history of Long QT Syndrome), or a family history of sudden cardiac death before age 40.

3.2.16 Participation in other therapeutic 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.

3.3 Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation. For restrictions related to concomitant medications, please refer to Section 8.2.

3.3.1 **Blood type and Indirect Antiglobulin Test (IAT) results**

CD38 is expressed at very low levels on erythrocytes. Preliminary data indicate that daratumumab interferes with IAT (also known as indirect Coombs test) testing and will make complete blood typing difficult while subjects are receiving treatment. In case of an urgent need for a blood transfusion, a blood sample should be obtained before the first infusion of daratumumab and the subject's blood type (ABO, Rh, and IAT) determined. Subjects should be provided a blood type card, which they will carry with them throughout the treatment period.

If the participating site's institution does not have a participant blood type card that they provide, please refer to Appendix G for a template to be printed and completed by the study staff, and given to the participant. Documentation of this process should be included in the source document.

3.4 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS)

OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

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

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at DFCI by the Research Project Manager. All sites should call the Lead Site Research Project Manager, by phone with any questions.

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 Lead Site 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 e-mail the Lead Site Research Project Manager, to verify eligibility. To complete the registration process, the Coordinator 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 coordinator will 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 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 Coordinating Center.

5. TREATMENT PLAN

5.1 Treatment Regimen

Daratumumab is to be administered as described in the table below per local standard of care. Reasons for early discontinuation of treatment are listed in Section 8.3.

Table 4: Daratumumab Treatment Regimen

Agent	Pre-medications/ Precautions	Dose	Route	Schedule	Cycle Length
Daratumumab	Please see section 5.2.1.3 for a list of pre-medications and post-medications	16 mg/kg	Intravenous	Q1 Week Cycles 1-2	4 Weeks
				Q2 Weeks Cycles 3-6	
				Q4 Weeks Cycles 7-20	

There is no maintenance therapy. Assessment of myeloma and progression will be performed at the beginning of each cycle, EOT, and every 3 months thereafter.

5.2 Agent Administration

5.2.1 **Daratumumab**

5.2.1.1 Daratumumab Preparation

The infusion solution will be prepared on the day of the planned infusion. Please see section 11.1 for detailed instructions for preparation of daratumumab.

5.2.1.2 Daratumumab Administration

Daratumumab (16 mg/kg) will be administered by IV infusion to subjects:

- Weekly during cycles 1 and 2
- Every other week during cycles 3 through 6
- Monthly during cycles 7 through 20

Each subject's dose will be calculated per local institutional standards. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. Subjects will receive pre-infusion medications and post-infusion medications as outlined in Section 5.2.1.3. Every effort should be made to keep subjects on the planned dosing schedule.

Please see Section 11.1 and site SOPs for administration of commercial daratumumab for full detailed instructions for administration of daratumumab.

5.2.1.3 Guidelines for Prevention of Infusion Reactions

Pre-Infusion Medication

Pre-infusion medications for subjects receiving daratumumab should be administered as described in Table 5 at the minimum, however sites may follow local guidelines for pre-infusion medications if more robust. On daratumumab infusion days, subjects should receive the following medications prior to infusion:

- Paracetamol (acetaminophen) 650-1000 mg IV or orally (PO) approximately 1 hour prior to daratumumab infusion.
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent) approximately 1 hour prior to daratumumab infusion.
- Approximately 1 hour prior to daratumumab infusion, methylprednisolone IV 100 mg for the first 2 infusions, 60 mg for all subsequent infusions (in the absence of infusion related AEs in the first 2 infusions). An equivalent intermediate-acting or a long-acting corticosteroid may substitute. IV administration is required prior to the first 2 infusions, but oral steroids may be substituted with subsequent infusions.

Post-Infusion Medication

For the prevention of delayed infusion-related reactions, all subjects are recommended to receive corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) 24 hours and 48 hours following daratumumab infusions for the first cycle of therapy, after which it is at the treating physician's discretion. Sites should follow the above and below outlined post-infusion medications at the minimum, however sites may follow local guidelines for post-infusion medications if more robust.

For subjects with higher risk of respiratory complications (ie, subjects who have a FEV1 <80% or subjects with asthma), the following post-infusion medications are recommended:

- Antihistamine (diphenhydramine or equivalent) 24 hours and 48 hours following all daratumumab infusions

- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salbumatol ± inhaled corticosteroids for subjects with COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight (under 24 hours) only for observation, then the hospitalization should not be reported as a serious adverse event (SAE). Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the hospital/clinic. If, after 4 full doses, an at-risk subject experiences no major infusion-related reactions, then post-infusion medications may be stopped at the investigator's discretion.

Table 5: Time and Events Schedule for Pre- and Post-Infusion Medication

Cycle (each cycle is 4 weeks in length)		Cycle 1				Cycle 2				Cycle 3 - 6		Cycle 7 - 20
Day During Cycle		D1	D8	D15	D22	D1	D8	D15	D22	D1	D15	D1
Study Drug Administration Refer to Section 11.1 for recommendations on daratumumab infusion rate.												
Daratumumab Administration		X	X	X	X	X	X	X	X	X	X	X
Pre-Infusion Medications												
Methylprednisolone (IV)	Methylprednisolone 100 mg for first 2 infusions, 60 mg for all subsequent infusions. Substitutions allowed.	approximately 1 hr prior to every infusion of daratumumab										
Antihistamine (IV or PO)	Diphenhydramine 25-50 mg or equivalent	approximately 1 hr prior to every infusion of daratumumab										
Paracetamol (IV or PO)	Paracetamol or acetaminophen 650-1000 mg	approximately 1 hr prior to every infusion of daratumumab										
Post-Infusion Medications												
Methylprednisolone (PO)	Methylprednisolone 20 mg/day orally or equivalent	24 hours and 48 hours days following daratumumab infusions in cycle 1 (beginning the day after the infusion). Treatment with methylprednisolone 24 hours and 48 hours following infusion after the first cycle is at the discretion of the treating physician.										
Antihistamine (PO)	Antihistamine (diphenhydramine or equivalent) 24 and 48 hours following all daratumumab infusions	For subjects with higher risk of respiratory complications (ie, subjects who have a FEV1 <80% or subjects with asthma), the following post-infusion medications are recommended. If, after 4 full doses, an at-risk subject experiences no major infusion-related reactions, then post-infusion medications may be stopped at the investigator's discretion.										
β2 adrenergic receptor (INH)	Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol											
Control Medications for lung disease (INH)	Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salbumatol ± inhaled corticosteroids for subjects with COPD)											

5.2.1.4 Management of Infusion-Related Reactions

Subjects should be carefully observed during daratumumab infusions. Trained study staff at the clinic should be prepared to intervene in case of any infusion reactions occurring, and resources necessary for resuscitation (eg, agents such as epinephrine and aerosolized bronchodilator, also medical equipment such as oxygen tanks and a defibrillator) should be available at the bedside. Attention to staffing should be considered when multiple subjects will be dosed at the same time.

If an infusion-related reaction develops, then the infusion should be temporarily interrupted or slowed down. Subjects who experience AEs during the infusion should be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply:

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab should be administered to the subject. Aggressive symptomatic treatment should be applied.

If an infusion is paused or the infusion rate is decreased, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as an SAE. However, if the underlying cause of the delayed infusion time is an AE or SAE, then that should be reported as such.

Infusion-Related Events of Grade 1 or Grade 2

If the site investigator assesses an AE to be related to the daratumumab infusion, then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the site investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased at the site investigator's discretion.

If the subject experiences a Grade 2 or higher event of laryngeal edema or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from the onset, then the subject should be withdrawn from treatment after discussion with the overall principal investigator.

Infusion-Related Reactions of Grade 3 or Higher

For infusion-related AEs that are Grade 3 or higher, the daratumumab infusion should be stopped, and the subject should be observed carefully until the resolution of the AE or until the intensity of the event decreases to Grade 1. The subject must be withdrawn from treatment after discussion with the overall principal investigator.

5.2.1.5 Hepatitis B Virus Serology Testing, and Management

HBV Serology

All subjects will be tested locally for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) at Screening. Additionally, subjects who are currently in the treatment phase of the study who are within 6 months of starting study treatment when Protocol Amendment 11 is implemented will be required to have HBV serology performed locally upon signing the updated ICF.

HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose.

HBV DNA Tests:

Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV as specified in the Study Calendar (Section 10). Where required by local law, the results of HBV testing may be reported to the local health authorities.

Management of Hepatitis B Virus Reactivation

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation see Section 10.

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

Table 6: Testing and Monitoring

	Screening Phase	**Treatment Phase**		**Follow-up Phase**		**Notes**
	Within 42 days of registration	Day 1 of each cycle (28-day cycles)	EOT within 30 days of last dose	Up to 6 months	After 6 months: Testing per standard of care	
Laboratory Assessments						
Hepatitis B (HBV) serology	X					Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc). Refer to Section 5.2.1.5

HBV DNA testing	X	Q12W during treatment, at the End of Treatment Visit, and Q12W for up to 6 months after the last dose of study treatment	For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at Screening, HBV DNA testing by PCR must be performed locally. Refer to Section 5.2.1.5

6. DOSE DELAYS

Dose modification of daratumumab is not permitted, but dose delay is the primary method for managing daratumumab-related toxicities.

6.1 Daratumumab Toxicity Management

Refer to Section 5.2.1.4 for details on management of infusion-related reactions. If any of the following criteria are met, then the daratumumab infusion should be held (**delayed not omitted**) to allow for recovery from toxicity.

Hematologic Toxicities: For adverse hematologic events that are considered possibly, probably or definitely related to Daratumumab, the following criteria for retreatment and dose modification should be followed. Treatment may be delayed for a maximum of 14 days. Holds other than described below may occur at the investigator's discretion, after discussion with the overall principal investigator.

Table 7 Daratumumab Hematologic Toxicities

CTCAE 4.0 Category	CTCAE Grade	Daratumumab Dose Modification
Thrombocytopenia (with bleeding)	**≤ Grade 2**	Hold dose until resolved to ≤ Grade 1
	≥ Grade 3	Discontinue study medication
Febrile Neutropenia	**≤ Grade 2**	Hold dose until resolved to < Grade 1
	≥ Grade 3	Discontinue study medication
Neutropenia with Infection	**≤ Grade 2**	Hold dose until resolved to < Grade 1
	≥ Grade 3	Discontinue study medication
All other related toxicities not listed	**≤ Grade 2**	Hold dose until resolved to ≤ Grade 1

previously in this table	**≥ Grade 3**	Discontinue study medication

Non Hematologic Toxicity: For adverse non hematologic events that are considered to be possibly, probably or definitely related to daratumumab, the following criteria for retreatment and dose modification should be followed. The treating investigator should determine the clinical significance of laboratory values or radiographic findings and attribution to study medications before a treatment decision is made. Treatment may be delayed for a maximum of 14 days. Holds other than described below may occur at the investigator's discretion, after discussion with the overall principal investigator.

Table 8 Daratumumab Non-Hematologic Toxicities

CTCAE 4.0 Category	CTCAE Grade	Daratumumab Dose Modification
All non-hematologic toxicities:	**≤ Grade 2**	Hold dose until resolved to ≤ Grade 1
	≥ Grade 3	Discontinue study medication

6.2 Daratumumab Delays

Administration of daratumumab may be restarted upon recovery from toxicity to Grade 1 or below, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered. If more than 2 consecutive planned doses of daratumumab are delayed due to AEs, treatment should be permanently discontinued after discussion with the overall principal investigator.

If 2 consecutive doses of daratumumab are delayed for any reason other than AEs, this should be brought to the attention of the Principal Investigator at the earliest possible time and study treatment should be discontinued, unless, upon consultation with the overall Principal Investigator and the review of safety and efficacy, continuation is agreed upon. Documentation of this discussion should be placed in the research chart or medical record. Delays for vacations or non-AE related events may be held for a maximum of 7 days. If held for longer, a discussion with the overall PI must occur to discuss whether the participant may remain on study.

7. TREATMENT COMPLIANCE

Study drug (daratumumab) will be administered by qualified site staff and the details of each administration will be recorded in the electronic case report form (eCRF).

8. CONCOMITANT THERAPY

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 8.2. The overall principal investigator must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Routine systemic use of all concomitant medications should be collected and recorded in the source documents beginning at registration to 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment. AEs and SAEs will be recorded as per Section 9.5.

Antiviral prophylaxis is permitted if that is the participating institution's' standard procedure.

8.1 Permitted Therapies

Supportive management for infections is strongly recommended, including vaccination with pneumococcal vaccine before beginning treatment with daratumumab. Concurrent use of bisphosphonates is allowed. Management of infusion related reactions is also recommended, as discussed in Section 5.2.1.3. Other symptoms may be managed according to institutional guidelines however; medications that could potentially prolong the QT interval should be discussed with the overall principal investigator prior to administration.

8.2 Prohibited Therapies

Use of the prohibited treatments listed below during the study will result in discontinuation of study drug for subjects:

- Administration of commercially available agents or agents under investigation for SMM or MM such as bortezomib, thalidomide, or lenalidomide, etc.
- Other agents that target CD38.

8.3 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 20 cycles or until one of the following criteria applies:

- Progression to overt Multiple Myeloma as described in Section 2.1 Table 1
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)

- Participant decides to withdraw from the protocol therapy

- Participant demonstrates protocol non-compliance that, in the eyes of the investigator, jeopardizes patient safety or the endpoints of the trial.

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.
The reason for taking a participant off treatment, and the date the participant discontinued study treatment, must be documented in the case report form (CRF) and conveyed immediately to the Lead Site Research Project Manager.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Irene Ghobrial at telephone # [redacted]

8.4 Duration of Follow Up

Participants will be followed every 3 or 6 months (+/-28 days) for up to 5 years after end of treatment. We plan to capture progression free survival, second progression free survival as well as time to biochemical progression, and time to progression to active symptomatic MM and any subsequent therapies for MGUS, SMM or MM. . If travel to the main site is financially burdensome for the participant during maintenance, an alternate schedule may be approved after discussion with the Overall PI.

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

The following is required during the Active Follow Up period (for up to 5 years):

1. Physical exams are voluntary during this period
    a. Virtual visits/telehealth visits are acceptable
2. SPEP and Immunofixation
3. Serum Free Light Chains (SFLC)
4. UPEP and Immunofixation only for those where disease is tracked by the urine
5. Serum Immunoglobulin test
6. PET/CT assessments are strongly recommended yearly and is required at the time of suspected progression
    a. The same assessment modality should be used consistently across the duration of the trial

7. Bone marrow biopsies are and strongly recommended yearly after EOT and is required at the time of suspected progression
8. Research bone marrow samples will be collected at the time of any bone marrow biopsy/aspirate procedure
9. Research blood will be collected whenever an in person visit to the site occurs. Research blood samples that are not collected at time points in the collection calendar due to COVID precautions or q6 month follow up will not be considered violations unless it is missed at the time of suspected progression.
10. Response
11. CRAB/MDE Assessment
12. Bone marrow biopsy/aspirate results and cytogenetics/FISH if ordered
13. Scan results and modality

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

8.5 Criteria for Taking a Participant Off Study

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

- Lost to follow-up
- Completion of 5 years follow up
- Withdrawal of consent for data submission
- Participant non-compliance, or loss to follow up
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF) and conveyed immediately to the Lead Site Research Project Manager.

9. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

9.1 Definitions

9.1.1 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 4.0** will be used for this study.

9.1.2 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 suspected transmission of any infectious agent via a medicinal product
- 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.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that

results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

- [For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.]

Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

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 9.2) and the characteristics of an observed AE (Section 9.3) will determine whether the event requires expedited reporting **in addition** to routine reporting.

9.2 Expected Toxicities

9.2.1 Adverse Events List(s)

9.2.1.1 Adverse Event List of Daratumumab

In general, daratumumab is tolerated well. The most frequently reported adverse events (AEs) across the daratumumab program have been infusion-related reactions (IRRs) following single agent therapy. Among all subjects treated in ongoing studies (monotherapy and combination therapy), IRRs have been reported in 49% of subjects; among 156 subjects treated with 16 mg/kg daratumumab monotherapy in Studies GEN501 and MMY2002, the percentage of subjects with a reported IRR was identical (48%) to what was observed across all treated subjects. Ninety-five percent (95%) of those patients, who had an IRR, had it during the first infusion; 11% of patients had a reaction at more than one daratumumab infusion. Most of the reactions were mild or moderate, and ended by temporarily stopping the infusion and giving medicines to treat the side effect. The most frequently reported AEs (reported in ≥5% of subjects) reported as IRRs were rhinitis allergic (8%), cough (7%), and nasal congestion (6%). Among subjects treated with 16 mg/kg daratumumab monotherapy, the most commonly reported IRRs were nasal congestion (8%), cough (7%), and rhinitis allergic and throat irritation (5% each). Grade 3 or higher IRRs were reported in 5% of subjects treated with 16 mg/kg daratumumab as monotherapy, with bronchospasm and hypertension being the most frequently reported Grade 3 or higher IRRs

(1% each). Across all ongoing studies, bronchospasm was reported in 10 subjects. Early in daratumumab development, in Study GEN501, 2 cases of bronchospasm were reported 24-48 hours following the second full-dose infusion of daratumumab. With the exception of those 2 cases, which had a delayed onset, all other reported bronchospasm events occurred following the first dose. All of the events occurring during the infusion period resolved quickly after standard treatments were administered. The daratumumab infusion was restarted, and no new onset of bronchospasm occurred. Most of the subjects who experienced bronchospasm had underlying respiratory diseases (asthma, chronic obstructive pulmonary disease [COPD], and others).

Among the 156 subjects treated with 16 mg/kg daratumumab as monotherapy in Studies GEN501 and MMY2002, the most frequently reported AEs (reported in >10% of subjects) were fatigue (39%); anemia (27%); nausea (27%); back pain (23%); neutropenia (22%); cough (21%); pyrexia (21%); thrombocytopenia (20%); decreased appetite (15%); infection of the nose, sinuses, or throat (20% each). Grade 3 and higher AEs were reported in 33% of subjects treated with 16 mg/kg monotherapy daratumumab. The most frequently reported Grade 3 or higher AEs were lung infection (6%); decline in general physical health (3%); pyrexia (3%); and hypercalcemia (3%). All other Grade 3 and higher AEs were reported in <3% of subjects. No deaths due to daratumumab-related AEs have been reported in any ongoing study.

9.3 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 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 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.

9.4 Expedited Adverse Event Reporting

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

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution must abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, all unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution from the time of consent through 30 days after the last dose of the investigational agent.

9.5 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.

The lead site (sponsor) study team will submit SAEs to the DFCI IRB on behalf of the site. Participating sites must report the event to the lead site study team within the time specified in order to comply with the reporting window.

Other investigative sites will also 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 9- DF/HCC Reportable AEs			
Attribution	**Gr. 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days	24 hours*
Possible Probable Definite	Not required	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 except through routine reporting mechanisms (entry in the EDC)				
* 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. **** Events that are expected (event term), but were experienced at a more severe grade, or longer duration should also be reported, as this is considered unexpected				

The Sponsor/Lead site study team will submit SAE reports from outside institutions to the DFCI OHRS per 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 coordinating center must forward an SAE Form to Janssen within 24 hours and in accordance with the reporting procedures described in section 9.7.

9.5.1 Protocol-Specific Expedited Adverse Event Reporting Exclusions

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.

9.6 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.

9.7 Expedited Reporting to Janssen

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

Janssen Scientific Affairs, LLC
[redacted]

The written Individual Case Safety Report (ICSR) must be completed and supplied to Janssen by facsimile or e-mail within 24 hours of knowledge of the event. A MedWatch Form will be utilized for expedited reporting to Janssen.

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender

- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

9.8 Adverse Events of Special Interest

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- HBV Reactivation
- Other malignancies

Any Adverse Event of Special Interest that is to be reported to the COMPANY should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of knowledge of the event.**

9.9 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.

9.10 Routine Adverse Event Reporting

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

9.11 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf

For DARZALEX® (daratumumab), the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure

9.12 Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

9.13 SAEs, Adverse Events of Special Interest and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The coordinating center will transmit all SAEs, Adverse Events of Special Interest and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 9.7, Expedited Reporting to Janssen, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the coordinating center will submit an unblinded SAE or pregnancy exposure report to Janssen Scientific Affairs, LLC.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the coordinating center, **within 24 hours becoming aware**, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs, LLC Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, Adverse Events of Special Interest, serious ADR or special situation is required.

- The coordinating center is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in Section 9.7 within **24 hours of such report or correspondence being sent to applicable health authorities.**

9.14 Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

9.15 Product Quality Complaint (PQC)

A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected for any reports of failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by the coordinating center within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the coordinating center must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

9.16 Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC by the Overall Principal Investigator within 24 hours of becoming aware of the event using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the Overall Principal Investigator within 24 hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10. STUDY CALENDAR

Screening evaluations are to be conducted within 42 days prior to registration. 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 do not need to be repeated. 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	**During Treatment[1, 3]**				**Follow Up[18]**
Tests and procedures	**≤ 42 days prior to registration**	**Cycle 1-20 Day 1**	**Cycle 1-20 Intracycle on Days of Dosing**	**Clinically Indicated or to confirm CR[9]**	**End of Treatment[13]**	**Every 3-6 Months[22]**
History and exam, height, weight, vital signs. Performance Status	X	X			X	X
Toxicity Notation	X	X			X	
Hematology group (WBC w/ diff, PLT, Hgb, ANC)[1,10]	X	X	X		X	X
Chemistry[4, 10]	X	X	X		X	X
Direct & total bilirubin[2, 10]	X	X	X		X	
Blood Type and IAT Testing[14]	X					

HIV, HBV, HCV Testing [19,20]	X	X[20]			X[20]	X[20]
Free light chain assay[10]	X	X			X	X
Serum and Urine Immunofixation (SPEP and UPEP) with quantitative immunoglobulins[10, 11]	X	X[8]			X	X
Response Assessment[17]		X			X	X
β2M, CRP, LDH[10]	X	X	X		X	X
Metastatic Bone Survey and MRI of the Full Spine ***OR*** PET/CT[16]	X				X	X
EKG	X				X	
PFT [21]	X					
Serum or urine pregnancy test	X					
Unilateral bone marrow aspirate and biopsy[5]	X			X	X	X[12]
Research bone marrow aspirate[6]	X[5]			X[6]	X[6]	X[12]
Research Blood[7]	X[7]	X[7]		X[7]	X[7]	X
Research Buccal Swab[15]	X					

1- Cycle 1, Day 1 hematologic laboratory values need to meet eligibility criteria to begin treatment
2- Direct bilirubin to be obtained if total bilirubin is abnormal.
3- Scheduling allows for -2/ +7 days.
4- Chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, calcium, glucose, albumin, ALT (SGPT), total protein, AST (SGOT), total bilirubin, uric acid, alkaline phosphatase, magnesium, and phosphorus.
5- These procedures should also be done at any time during the course of the study to confirm CR, or as clinically indicated
6- Research bone marrow aspirate and biopsy at same time of clinically indicated bone marrow biopsy and to confirm response.
7- Peripheral blood samples for correlative studies.
8- SPEP with immunofixation and quantitative immunoglobulins should be performed at screening, cycles 1-20 day 1, EOT, and at each follow-up visit.
9- If confirmation of response BM biopsy/aspirate was performed within 12 weeks of subsequent time point listed; the aspirate need only be repeated.
10- For Cycle 1 Day 1, no need to repeat tests if they have been performed within the past 7 days. Testing may be performed up to 2 days before other infusion days. Results of hematology tests must be evaluated before each study drug administration. Perform at additional timepoints, as clinically indicated. To be done by local lab. Patients need only meet hematologic inclusion criteria to begin treatment on C1D1.
11- If the participant's disease response is not followed primarily via a UPEP and Urine immunofixation, these tests may be done only at screening, as clinically indicated during treatment, end of treatment, and as clinically indicated during follow-up.
12- Strongly recommended to be performed yearly after EOT during follow-up and is required when there is suspected clinical progression
13- End of Treatment Assessments should be performed 4 weeks (+/- 1 week) after the last dose of daratumumab
14- Participants should receive blood typing card per section 3.3.1, prior to first dose of therapy- If the participating institution does not have a card that it provides its patients, refer to Appendix G for a template for completion by the study team and given to each participant
15-Buccal swab(s) may be collected at any time during the study
16- If PET/CT results are concerning for myeloma involvement, a follow up MRI must be conducted to confirm eligibility (baseline) or progression (on study and in follow up) PET CT strongly recommended yearly after EOT during follow up and are required at time of suspected disease progression.
17- A response assessment is required starting on C2D1, and at cycle thereafter based on Day 1 values, at EOT, and at each follow up Day 1 until off study.
18- If travel to the main site is financially burdensome on the participant, an alternate follow up schedule may be approved after discussion with the Overall PI- Window for follow up visits is +/- 4 weeks (28 days)
19- Subjects who are currently in the treatment phase of the study who are within 6 months of starting study treatment when DFCI Protocol Amendment 11 is implemented will be required to have HBV serology performed locally upon signing the updated ICF- HBV serology and DNA testing is not required at screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to first dose of daratumumab.
20- HBV testing for those with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc)

at Screening, HBV DNA testing by PCR must be performed locally every 12 weeks during treatment, at the End of Treatment Visit, and every 12 weeks for up to 6 months (24 weeks) after the last dose of study treatment- Refer to 5.2.1.5
21- Only those who are known to have COPD (chronic obstructive pulmonary disease) or severe, persistent asthma, or thought to have compromised lung function must have a PFT to confirm eligible (must have a FEV1 <50% of predicted normal.)
22- Participants unable to participate in follow up every 3 months may follow up every 6 months at PI discretion in accordance with standard of care follow-up frequency and COVID precautions. Physical exams and correlative blood draws that are not done due to virtual visits will not be considered violations. Local myeloma labs must be provided to the participating site for data entry purposes. Bone marrow biopsy and scans are strongly recommended yearly after EOT but are required when there is suspicion of clinical progression. These assessments can be waived due to extenuating circumstances or for insurance coverage reasons. Scans and bone marrow biopsy and research samples are required at time of suspected disease progression if one is performed

11. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with Daratumumab can be found in Section 9.2.1.

11.1 Daratumumab

11.1.1 Physical Description of Study Drug

Daratumumab is supplied as a colorless to pale yellow preservative-free solution for intravenous infusion in single-dose vials. Daratumumab drug product is formulated as a concentrate of 20 mg/mL ± 2 mg/mL in an isotonic buffer consisting of sodium acetate, sodium chloride, mannitol and polysorbate 20 at pH 5.5. It will be manufactured and provided under the responsibility of Janssen. Study drug labels will contain information to meet the applicable regulatory requirements.

11.1.2 Storage and Stability

All study drug vials must be stored in the original carton in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Daratumumab does not contain preservatives; therefore any unused portion remaining in the vial must be discarded.

11.1.3 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.

11.1.4 Availability and Ordering

Daratumumab will be provided free of charge by Janssen Scientific Affairs, LLC as 400mg/20ml vials. Biologics, Inc. will provide drug distribution services for the study. In the event that 400mg/20mL vials are not available, Janssen Scientific Affairs, LLC will provide an equivalent formulation of daratumumab in 100mg vials as a substitute.

The Janssen Scientific Affairs internal study number is [redacted].

Biologics, Inc. contact details for drug ordering:
[redacted]

Throughout the course of the study, a Biologics, Inc. clinical hotline support, staffed with clinical pharmacists, is made available 24/7/365 in the event an investigator or site coordinator has a question.
Hotline phone#[redacted]

11.1.5 Preparation

Daratumumab will be diluted in a sterile, pyrogen-free physiological saline solution (0.9% NaCl) prior to IV administration in accordance with the site's standard operating procedures (SOPs) for commercial daratumumab.

11.1.6 Administration

Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used. Do not infuse daratumumab concomitantly in the same intravenous line with other agents. Infusion rate of daratumumab and infusion procedures should be in accordance with the site's SOPs for commercial daratumumab. The infusion of daratumumab should not exceed 15 hours.

For sites utilizing the rapid daratumumab infusion (Barr et al.) rate as part of their local institutional standards, please refer to Appendix F for guidance on preparation and administration.

11.1.7 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.)

11.1.8 Destruction and Return

The Drug Accountability Log will contain the date and amount of study drugs received, and unused vials destroyed. All used and partially used study drug will be destroyed by the site, in accordance with the site's SOPs. All expired vials of study drug will be destroyed by the site, in accordance with the site's SOPs.

12. BIOMARKER, CORRELATIVE, MRD ASSESSMENT, AND SPECIAL STUDIES

This trial will provide samples of high-risk MGUS and low-risk SMM patients treated with daratumumab to

comprehensively characterize the MM genome and immune cells function and define molecular events driving development and progression of MM.

We will attempt to obtain samples on all patients at the following time points: before therapy, day 1 of each cycle, end of treatment, every three months during follow up, at the time of response determination (CR) and 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. Samples will be kept until exhausted.

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

Peripheral blood and bone marrow derived mononuclear cells will undergo immunologic assessments to assess the impact of therapy on general measures of cellular immunity, MM reactive T cells, and antigen specific immunity. The percentage of circulating and bone marrow derived regulatory immune cells will be determined.

12.1 Minimal residual disease assessment (MRD)

Bone marrow samples will be collected per the collection time described in the table of sample collection (appendix b). Samples for MRD testing will be collected on all patients who achieve a VGPR or better in treatment or during follow-up at the specified timepoints laid out in Appendix B.

MRD will be assessed using Adaptive's LymphoSIGHT platform as part of normal clinical care for Dana-Farber Cancer Institute patients only in patients that experience a Very Good Partial Response or better. Bone marrow samples will be collected per the collection time described in the sample collection table. The samples will be prepared in the Ghobrial lab and sent for testing in bulk by Adaptive at an undetermined time during the study for analysis.

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 bone marrow. 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 destroy the samples after exhaustion of the DNA.

12.2 Correlative Studies

Correlative studies will be performed to determine:

1. Clonal evolution during therapy and at time of progression (using whole exome sequencing)
2. Immune cell activity and numbers before therapy and during therapy

12.2.1 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[10,56]. Briefly, somatic single nucleotide variants are determined using the MuTect algorithm[57]. 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[58]. 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[59], and open vs. closed chromatin status[60]. Focal as well as arm-level copy number variations will be determined based on whole exome sequencing and subsequent application of the GISTIC algorithm[61].

The DNA library will be prepared at the Ghobrial Lab, and then sequencing will be done at the following external lab:

Broad Institute Genomics Services

[redacted]

Sequencing data will then be provided back to Ghobrial lab in the form of BAM file. The samples that are sent for analysis are exhausted during the process, and thus not able to be returned.

12.2.2 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[62,63-65]. 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[63-65].

The DNA library will be prepared at the Ghobrial Lab, and then sequencing will be done at the following external lab:

Broad Institute Genomics Services

[redacted]

Sequencing data will then be provided back to Ghobrial lab in the form of BAM file. The samples that are sent for analysis are exhausted during the process, and thus not able to be returned.

12.2.3 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 at DFCI. Each cell type will be defined by unique combinations of antibodies based on previous publications[66,67]. 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. CD38 expression in these immune cell subpopulations will be examined, and the CD38+ groups will be evaluated for response to daratumumab. 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.

12.2.4 T cell specific responses

Previous daratumumab clinical studies in myeloma have demonstrated robust T cell changes in the daratumumab treated patients, with significant CD8+ T cell expansion that was higher in responding patients compared to non-responders. In addition, naïve CD8+ T cells decreased, and central memory CD8+ T cells increased. T cell clonality was monitored by TCR sequencing (Immunoseq^{TM}) and significantly increased with daratumumab treatment. Responders had significantly higher changes in clonality compared to non-responders. In addition, CD38+ immune suppressive cells (regulatory T cells, MDSC) were noted to decrease with daratumumab treatment. This data suggests that daratumumab may increase the adaptive immune response against malignant disease, and in patients with pre-malignancy who are treatment naïve, this immune response could be even more robust. Therefore, we will examine the T cell response to daratumumab treatment in this study through in depth immunophenotyping (flow or CyTOF), functional studies examining T cell response pre- and post-daratumumab treatment.

12.2.5 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 and submitted for RNA sequencing as described above.

The RNA library will be prepared at the Ghobrial Lab, and then sequencing will be done at the following external lab:

Broad Institute Genomics Services

[redacted]

[redacted]

Sequencing data will then be provided back to Ghobrial lab in the form of BAM file. The samples that are sent for analysis are exhausted during the process, and thus not able to be returned.

12.3 Bone Marrow Aspirate Samples

Collection of bone marrow aspirate specimens for exploratory analysis is voluntary for this study and will be obtained at the times of bone marrow collections. Specimens will be shipped (via traceable carrier) to and subsequently processed, analyzed, and stored at Dana-Farber Cancer Institute.

12.3.1 Specimens Required

- 2 Purple Top Tubes (EDTA), 10mL each. At certain timepoints, an additional 3ml Purple Top Tube (EDTA) is requested. Specimens should be collected on Mondays to Thursdays for same-day shipment.

12.3.2 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 or UPS next day or overnight delivery the same day the sample was collected. Please only ship Monday-Thursday.

12.3.3 Shipping Information

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

12.3.4 Shipping Instructions:

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

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

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

3. Please email the Lead Site Research Project Manager to notify of an incoming shipment.

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

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

   Dana-Farber Cancer Institute
   Ghobrial Lab
   [redacted]
   Email: [redacted] Please retain a copy for site record maintenance.

Please see Appendix B and Appendix C for Collection Schedule and Requisition Form.

12.4 Peripheral Blood Samples

Collection of peripheral blood specimens (including serum and plasma) for exploratory analysis is voluntary for this trial. Please see Appendix B for a list of timepoints and specific instructions. These collections will be taken at the time of routine blood collection timepoints required for this study. Specimens will be processed on site according to instructions below and shipped (via traceable carrier) to Dana-Farber Cancer Institute. Once the shipment is received, samples will be subsequently processed, analyzed, and stored at Dana-Farber.

12.4.1 Specimens Required

- 2-3 x 10 mL Purple Top Tubes (K2EDTA) and 1 x 6mL Red Top Tube must be collected Mondays to Thursdays for same-day shipment.

12.4.2 Shipping Information

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

12.4.3 Shipping Instructions:

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

12.4.4 Processing Information:

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

Package tubes at room temperature and wrap in a liberal amount of paper towel around the tubes to ensure adequate insulation of the specimen(s) and absorption in the event of a breakage. Place wrapped specimen in a biohazard labeled Ziploc bag with a fridge pack and zip close. Wrap bubble wrap around the bag and place in a cardboard box. If space remains in the box, stuff with extra paper towel to reduce shifting of samples. Complete

the shipping requisition form using the address listed below. Prepare the package for shipping, applying packing tape as needed. Ship the package using FedEx or UPS next day or overnight delivery the same day the sample was collected. Please only ship Monday-Thursday.

With each shipment, please include the following:

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

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

3. Please email the Lead Site Research Project Manager to notify of an incoming shipment.

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

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

   Dana-Farber Cancer Institute
   Ghobrial Lab
   [redacted]

   Please retain a copy for site record maintenance.

13. MEASUREMENT OF EFFECT

13.1 Development of symptomatic disease

In this study, patients may continue on study until the development of symptomatic MM that requires therapy. This is defined as one of the following criteria (CRAB and Myeloma defining events< MDE):

- Increased calcium levels (corrected serum calcium >0.25 mmol/dL above the upper limit of normal or >0.275 mmol/dL) due to myeloma
- Renal insufficiency (attributable to myeloma);
- Anemia (Hb 2g/dL below the lower limit of normal or <10 g/dL) due to myeloma
- Bone lesions (lytic lesions or generalized osteoporosis with compression fractures)
- Or any MYELOMA DEFINING EVENTS (MDE) as follows:
  - Clonal bone marrow plasma cell percentage ≥ 60%[20]
  - An abnormal FLC-ratio ≥100 (involved kappa) or <0.01 (involved lambda)[21]
  - >1 focal lesions (≥5mm) on MRI or PET-CT studies[22,23]

For measurement of response:

The disease response will be assessed using criteria based on the International Working Group Uniform Response Criteria in Section 14.2.2.1. If the only measurable parameter is serum immunoglobulins free light chain (FLC), the participant will be followed by IMWG Response Criteria provided in Section 13.2.2.2

Disease response by the Modified EBMT Response Criteria in Section 13.2.2.3 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.

13.2 Antitumor Effect

13.2.1 Methods for Evaluation of Disease

All baseline evaluations should be performed on Cycle 1, Day 1 (Week 1) of initial therapy. Response will be assessed at at each cycle, at the end of treatment visit, and every 3 months (follow up) thereafter. Response will be assessed by M-protein quantification, protein electrophoresis and immunofixation from serum and a 24-hour urine collection (unless participants are not measured for response in their urine), A serum sample for free light chain ratio testing will be obtained. In addition, bone marrow aspiration and biopsy, as well as skeletal survey/PET-CT/MRI will be performed to determine overall response or confirm response. Evaluations should be performed as determined by the Study Calendar, Section 10.

Daratumumab, as an immunoglobulin, may interfere with clinical SPE/IFE assessments. In cases where daratumumab interference is suspected, a reflex assay (DIRA: Daratumumab- specific Interference Reflex Assay) confirming the presence of daratumumab will be performed. In cases where CR or sCR is suspected and DIRA confirms that daratumumab is present on SPE/IFE, additional clinical assessments will be triggered to confirm the CR/sCR. A patient who meets all other clinical criteria for CR/sCR, and who has daratumumab interference confirmed by the reflex assay, will be considered a CR/sCR.

13.2.2 Response Criteria

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

13.2.2.1 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 <100 mg per 24 hours.
Partial Response (PR)	≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg 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.

*Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.
†Clarifications for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. The "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

13.2.2.2 Modified EBMT Disease Response Criteria

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

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

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

a Based on the criteria reported by Blade et al., 1998.
b Per Blade *et al*., 1998, if absence of the monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow except in participants with nonsecretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
c Per Blade *et al*., 1998, skeletal X-Rays are not required for the definition of response, but if performed there must be no evidence of progression of bone disease (no increase in size or number of lytic bone lesions).

d It is suggested that the reference point for calculating any increase should be the lowest value of the preceding confirmed response (MR, PR or CR) or the baseline value if there is no previous confirmed response.
e Other clinical data may be requested by the IRC, as necessary, to assess the cause of the hypercalcemia.

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

We will measure MRD via Adaptive's LymphoSIGHT platform in Dana-Farber Cancer Institute patients who achieve VGPR or better to determine the number of patients who are MRD negative vs MRD positive.

13.2.3.1 MRD Analysis

MRD will be performed via LymphoSIGHT, flow cytometry, or both.

MRD will be carried out according to the LymphoSIGHT™ method (Adaptive Inc,) using clinical bone marrow aspirate samples[66]. Prior studies have compared this technique to the traditional MRD immunofluorescence technique, as previously reported [67] 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

13.2.4 Duration of Response and Endpoint Definitions

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

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

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

13.2.5 Progression-Free Survival

Progression-Free Survival (PFS): PFS is defined as the time from first-dose 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.

13.2.6 Response Review

Central review of disease response assessments is not planned.

14. 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).

14.1 Data Reporting

14.1.1 Method

The Office of Data Quality will collect, manage, and perform quality checks on the data for this study.

14.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality according to the schedule set by ODQ. **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.**

14.2 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.

15. STATISTICAL CONSIDERATIONS

The primary objective of this study is to determine the proportion of patients who are in VGPR or better after therapy with Daratumumab. Secondary objectives include safety, duration of response and MRD negative rate.

Correlative objectives include correlative immune cell regulation and clonal evolution.

15.1 Study Design/Endpoints

The primary endpoint of this study is to determine the proportion of patients with high-risk MGUS and low-risk smoldering multiple myeloma (SMM) patients who have a deep response (defined as VGPR or better) to daratumumab. Secondary endpoints include toxicity rates, MRD negative rate, and duration of response. Correlative objectives are to a) evaluate clonal heterogeneity using deep sequencing at the DNA and RNA level and determine association of genomic aberrations with response/progression to daratumumab and progression to SMM/MM, b) evaluate T cell response (flow cytometry, TCR sequencing, functional T cell status) in this patient population, c) assess changes in the immune microenvironment in high-risk MGUS patients over the course of the study; to assess these immune changes and association with progression to SMM or MM, d) examine the immunoglobulin sequence in MGUS and SMM patients to determine if common clonal sequences are noted among high-risk MGUS and low-risk SMM, and to evaluate whether common Ig sequences are associated with progression and e) assess the rate of secondary hematologic malignancies.

Fifty patients will be entered on study. The criteria used to determine the treatment is promising that the lower limit of the two-sided 90% binomial confidence interval for the deep response rate is at least 50%. Given that this group of patients is usually not treated, the design is such that the true deep response rate is at least 50%. If an observed deep response (VGPR or better) rate is 64% (≥ 32/50 patients) the treatment will be considered promising. The power to detect a treatment effect was computed assuming a response rate of 70% or 75%. In these two scenarios, the power is equal to 86% and 97% (with type I errors of 0.03).

15.1.1 Analysis of Primary Endpoint

The primary endpoint is the proportion of patients in deep response (VGPR or better). The estimate and the two-sided 90% binomial confidence interval will be provided in the analysis.

15.1.2 Analysis of Secondary Endpoints

The objective response rate (partial response or better according to the modified IMWG criteria) and the proportion of patients that are MRD negative, CR, PR or MR will be reported with 90% exact binominal confidence interval (CI).

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) the Kaplan-Meier method will be used.

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.

15.2 Sample Size, Accrual Rate and Study Duration

A total of 50 eligible patients will be enrolled. We expect 2 years of active accrual (approximately 2 patients per month) and 5 years of follow-up of patients.

15.3 Stratification Factors

There are no stratification factors.

15.4 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.

15.5 Stopping Rule for Safety

All participants will be evaluable for treatment-related toxicity from the time of therapy initiation. The severe adverse event (SAE) is defined as any grade 3 adverse events that affect organ function (cardiac, hepatic, thromboembolic) or grade 4/5 non-hematologic AEs. We anticipate that the rate of SAE is low in this study population and there is no pre-defined stopping rule for safety.

16. PUBLICATION PLAN

The results should be made public within 12 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 two (2) years after the end of the study. Data sets from other relevant studies such as 14-338, 16-313, or data from other collaborators may be used and/or analyzed for the purposes of the publication.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: SPECIMEN COLLECTION SCHEDULE

Sample Time Point[3]	Recipient	Sample Type	Shipping Method	Container[1]
Baseline	DFCI	Peripheral Blood	Fridge pack same day	3x 10mL Purple Top 1x6ml Red Top
		Bone Marrow Aspirate		2x10mL Purple Top 1x3ml Purple Top
		Buccal Swab[2]	Ambient same day	2x Buccal Swab
Cycle 1 – 20 Day 1 (Pre- Dose)	DFCI	Peripheral Blood	Fridge pack same day	2x10mL Purple Top 1x6ml Red Top[3]
Annually (Yearly from EOT +/-28 days)	DFCI	Bone Marrow Aspirate	Fridge pack same day	2x10mL Purple Top 1x3ml Purple Top
		Peripheral Blood		3 x 10mL Purple Top 1 x 6ml Red Top
Confirm Response[4]	DFCI	Peripheral Blood	Fridge pack same day	3x 10mL Purple Top 1x6ml Red Top
		Bone Marrow Aspirate		2x10mL Purple Top 1x3ml Purple Top
End of Treatment and/or Disease Progression	DFCI	Peripheral Blood	Fridge pack same day	3 x 10mL Purple Top 1 x 6ml Red Top
		Bone Marrow Aspirate		2 x10mL Purple Top 1 x 3mL Purple Top
Follow-up[5] (Blood samples will be collected every 3 or 6 months +/- 28 days)	DFCI	Peripheral Blood	Fridge pack same day Same day	3 x 10mL Purple Top 1 x 6ml Red Top
		Bone Marrow Aspirate[5]		2 x10mL Purple Top 1 x 3mL Purple Top
Clinically Indicated and/or Yearly Bone Marrow Biopsy/Aspirate	DFCI	Bone Marrow Aspirate	Fridge pack same day	2x10mL Purple Top 1 x 3mL Purple Top
		Peripheral Blood		3 x 10mL Purple Top 1 x 6ml Red Top

[1] Purple Top= K2EDTA Tube; Red Top= No Additive
[2] Buccal swabs can be collected at any point while on the study- Two swabs may be taken to ensure collection of cells
[3] Samples at all time points are voluntary, and do not exclude patients from treatment
[4] For this study, VGPR or CR- For definition of Response, please refer to section 13.2.2.
[5] During follow up, bone marrow aspirate procedures are requested yearly from the time of EOT

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 [redacted] to alert study team of shipment and include tracking number and requisition form the day of shipment.

Ship specimen(s) to: Dana Farber Cancer Institute
Ghobrial Lab
[redacted]

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	_____Red Top _____Purple Top _____Buccal Swab/ Oragene Kit		
☐ Cycle _____	☐ Blood	_____Red Top Purple Top		
☐ Follow-Up_____	☐ Blood ☐ Aspirate	_____Red Top Purple Top		
☐ Confirm Response _____	☐ Blood ☐ Aspirate	_____Red Top Purple Top		
☐ End of Treatment ☐ Disease Progression	☐ Blood ☐ Aspirate	_____Red Top Purple Top		
☐ Clinical Necessity/ Standard of Care	☐ Aspirate	_____Purple Top		

Responsible Contact: _____ **Email:** _____

Site: _____ **Phone number:** _____

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

APPENDIX D: DANA-FARBER/ HARVARD CANCER CENTER MULTI-CENTER OVERSIGHT PLAN AND DATA SAFETY MONITORING PLAN

Version 2 7.28.2017

DFCI IRB Protocol #:17-212

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 (i.e. FDA). 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 M. 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. A current CV will be collected at study initiation.
- 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, as well as current Investigator Brochure or product information.
- 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. All site Principal Investigators will sign protocol signature pages at study initiation and each protocol version change.
- 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 (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials), as applicable. All tasks delegated by the Sponsor-Investigator to the CRO will be detailed to the appropriate regulatory authority, as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.

- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

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

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions 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. Source data will be maintained and Case Report Forms (CRFs) will be verified with source data, as applicable.
- 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 as listed in the IP Management Plan.
- 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. The informed consent will be explained to each subject and signed and dated by the subject prior to participation in the study. The consent will be retained on file by the investigator.

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

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and e-mailed to the Lead Site Research Project Manager at the Coordinating Center

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

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, and, if applicable, assigned treatment and/or dose level.

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.

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 process for requesting an eligibility exception is defined below.

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 *9.*

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 *11*.

Participating Institutions should order their own agent regardless of the supplier. (i.e., NCI or a pharmaceutical company.) Janssen Scientific Affairs, LLC will supply the investigational agent. A drug distribution vendor will be engaged for ordering and re-supply at each individual site.

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

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the 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 Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring 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.

Additionally, regular and ongoing communication with Participating Institutions will be accomplished by holding all site teleconferences at quarterly until enrollment is completed and the last participant in has been on study for at least 6 months. After this there will be teleconferences every 6 months until all participants are off treatment. Additional teleconferences will take place as needed for significant events (i.e. change in accrual, event involving participant, etc.) 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 Monitoring

Participating Institutions will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification. Each participant's initial consent and eligibility will be reviewed within 30 days of enrollment. Study visits and corresponding CRFs will be reviewed every 6 months for protocol compliance, AEs, SAEs, study drug administration, dose modifications, and follow-up of action items. Pharmacy records will be remotely reviewed every 6 months.

On-Site Monitoring

Participating Institutions will have annual on-site visits to for a Pharmacy site review, Regulatory binder review, and to meet with the site PI (if available).

Closeout Monitoring

Closeout monitoring will be done remotely at the end of the study.

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. Monitoring logs will be maintained to ensure monitoring activities are adequately documented.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. Due to the small patient population, the accrual minimum requirement is at least 1 patient every two years.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance 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 and the 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.

APPENDIX E: INVESTIGATIONAL PRODUCT MANAGEMENT PLAN

A Phase II Study of the CD38 Antibody Daratumumab in Patients with High-Risk MGUS and Low-Risk Smoldering Multiple Myeloma

Overall Principal Investigator: Irene M. Ghobrial, MD
Coordinating Center: Dana-Farber Cancer Institute

Version 3.4
Version Date September 10th[t], 2019

1. IP Forecasts

1.1 IP projections for the duration of the IIS

Patients will be treated with daratumumab at a dose level of 16mg/kg on the following schedule:

Cycle	Dosing Schedule
Cycle 1-2	Days 1, 8, 15, 22
Cycle 3-6	Days 1, 15
Cycle 7-20	Day 1

Dosing will be an IV infusion following the guidance for commercial daratumumab administration outlined in the United States Package Insert as well as according to site policy. Each cycle will be 28 days.

With an expected accrual of 50 patients, all of whom will receive daratumumab as detailed above, the projected product requirement for this study is as follows:

- Assuming 4 vials per dose and a patient weight of 100kg: 400mg vials
- Daratumumab: 4 vials of 400mg x 30 doses x 50 patients = 6,000 vials

Drug	Vials/ Dose	Total Doses	# of Patients	Vials/ Patient	Total Vials	10% Overage	20% Overage
Daratumumab	4	30	50	120	6000	6600	720

- Assuming 16 vials per dose and a patient weight of 100kg: 100mg vials
- Daratumumab: 16 vials of 100mg x 30 doses x 50 patients = 24,000 vials

Drug	Vials/ Dose	Total Doses	# of Patients	Vials/ Patient	Total Vials	10% Overage	20% Overage
Daratumumab	16	30	50	480	24,000	26,400	28,800

1.2 Overall plan per Quarter for IP requirements (inclusive of each participating site, over-all subject enrollment rate, current inventory and expiring IP at each site)

The study team anticipates an accrual of 2 patients/ month (approximately 6 patients per quarter) to complete accrual of 50 patients in 25 months. Each patient will be dispensed study drug at the timepoints described in section 1.1 of this IP Management Plan. Each subsite will be allowed to maintain IP dispensation and accountability records per their individual site SOPs. Dana-Farber Cancer Institute, as the coordinating center will review each sites SOPs to ensure they comply with GCP and ICH guidelines. Each subsite will maintain drug destruction records per their sites individual SOPs. Dana-Farber Cancer Institute, as the coordinating center, will collect all pharmacy records at the completion of the study.

1.3 Process to re-evaluate IP requirements (inclusive of all participating sites)

DFCI will submit monthly enrollment information to Janssen Scientific Affairs, LLC. The study team will inform the pharmacy when a new patient is enrolled. Biologics, Inc., the drug distribution center, will provide monthly dispensing and accountability reports to Janssen Scientific Affairs, LLC and Dana-Farber Cancer Institute.

2. Inventory Control

2.1 Record of receipt and disposition of IP

Biologics, Inc.,the drug distribution center, will receive and check all incoming shipments with proper documentation, enter into a 21CFR Part 11 compliant system, and place in proper and monitored storage. Upon destruction, or return of study drug, all documents are completed, accountability logs are signed off on and closed, and drug is disposed of or returned properly.

Biologics, Inc. will ship the study drug to each participating site. All study drug will be shipped in original manufacturer's packaging with a protocol-specific label adhered to the outer packaging. Study Drug is shipped in a Biologics branded package with appropriate materials to maintain temperature stability. All drug orders are shipped via *FedEx for Priority Overnight* delivery for shipments to US sites.

Each shipment includes a label on the Ziploc bags with the following information:

- The Study Number
- IND caution statement and/or local regulatory statements
- Drug identification
- Lot Number
- Expiration date
- Dosing instructions (i.e., "Administer as Directed per Protocol")
- Storage instructions (i.e., "Store at controlled refrigerated temperature, 2-8°C")
- Emergency contact instructions

For all shipments from Biologics:

- A complete accountability record including date of dispense, site name, quantity dispensed, and balance forward will be recorded. Study accountability records are documented in electronic 21 CFR format and are kept in a secured area for duration of the study.
- Provide a Pharmacist review; a licensed pharmacist checks off package for accuracy of contents, authorizing order via 21 CFR compliant trial accountability log.
- Enclose a packing slip that includes the quantity of drug provided with a section to be completed once received by the site coordinator. This section includes confirmation of drug receipt, verification of package contents, and instruction to fax the completed packing slip to Biologics.
- Process and ship authorized and completed orders "same day" of receipt if received before 2:00 p.m. ET Monday through Thursday. Authorized and completed orders received after 2:00 pm ET Monday through Thursday will be processed and shipped the next business morning.
- Packages are tracked until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator for all shipments.

DFCI will receive and check all incoming shipments with proper documentation. DFCI keeps the shipping receipt and records the disposition of the drug. DFCI will place all received shipments in proper and monitored storage. Upon destruction of study drug, all documents are completed, accountability logs are signed off on and closed, and drug is disposed of properly.

Each participating sub-site will maintain records of drug accountability and destruction according to their local SOPs, which will be reviewed by the coordinating center for compliance with GCP and ICH guidelines.

2.2 **Periodic review and documentation of current supply of all IP**

Biologics will effectively manage inventory to reduce waste due to expiration issues through strict adherence to FIFO inventory procedures, just in time inventory management, and end of day and monthly audits.

Each day Biologics will perform an end of day audit for all trial specific drugs that were dispensed on that particular day. The end of day audit reconciles the physical shelf inventory to accountability records. During the monthly inventory report Biologics personnel will compare shelf inventory against the balance as stated on the drug accountability report. Perpetual inventory audits are documented via 21 CFR Part 11 compliant accountability records throughout the duration of the study and with oversight by the Director of Clinical Trial Services.

The DFCI pharmacy routinely reviews the amount of IP on site and re-orders as needed based on current enrollment.

2.3 Plan for resupply of IP based upon overall IIS use and/or expiration of IP

Biologics, Inc. will request resupply as needed based on inventory level and expiry dates from Janssen Scientific Affairs. The coordinating center will liaise with the drug distribution center as needed based on drug supply levels via telephone or email to review currently supply and expiry dates

Each individual sub-site will measure drug supply levels and forecast needed drug supply based on local practice.

2.4 System to quarantine and control expired or recalled IP

All study product that requires quarantine will immediately be recorded in the accountability record, moved from general storage, placed into a secure quarantined area separate from other study drug. Janssen Scientific Affairs, LLC will be notified and the supply will be handled as required.

3. Storage

3.1 IP storage conditions

All participating sites are required to maintain adequate accountability and storage of investigational agents as specified in the study protocol and the study data safety monitoring plan. Each individual sub-site may store IP per their local SOP for storage procedures for investigational drug supply.

Biologics, Inc. will store the study drug in secure temperature and humidity controlled storage for the duration of the study. Drug and the accountability log is reviewed and signed off by the qualified personnel as outlined in Biologics operating procedures. This quality check is documented via Clinical Trial Material Accountability/Quality Assurance Log (Receipt) and the document is then stored in the trial files for the duration of the study. All study drugs will be stored at controlled temperatures until shipment with access limited to essential personnel only.

Daratumumab will be stored at controlled refrigerated temperatures of 2-8°C. Biologics will assume receipt of one study drug supply on at least a quarterly basis. Temperature and humidity monitoring that is 21 CRF Part 11 compliant is provided 24/7/365 throughout the duration of the study. During non-operational hours, electronic surveillance alerts Biologics after-hour's response personnel to out of range fluctuations in temperature and humidity. Biologics will provide temperature monitoring reports upon request. Temperature excursions will be communicated to the manufacturer & Coordinating Center to provide an assessment of affected drug supplies.

Biologics will maintain separate inventories for protocol-specific drug supplies.

Inventory Maintenance includes:

- Separate physical locations with shelf labeling
- Study, Drug, Strength, Expiration shelf labeling
- Inventory management within Biologics information system
- Inventory reports on agreed fields submitted on agreed schedule

DFCI will store the study drug in secure temperature and humidity controlled storage for the duration of the study. All study drugs will be stored at controlled temperatures until shipment with access limited to essential personnel only.

3.2 Plan for maintaining documentation of proper storage conditions according to the package insert/IP guidelines

Biologics, Inc. will include proper storage and drug usage information on packing slips and auxiliary documents in all shipments sent to the study sites.

Proper storage and drug usage information is contained in section 8 of the protocol. All participating sites are required to maintain adequate accountability and storage of investigational agents as specified in the study protocol and the study data safety and monitoring plan.

Each individual sub-site may follow their local SOP for maintaining documentation of drug supply. Each site's SOP will be reviewed by the coordinating center to ensure it complies with GCP and ICH guidelines.

3.3 IP storage separate from non-clinical material, in secure location and limited access

Prior to distribution, the IP will remain separate from other study drugs and will be stored in a secure facility at the drug distribution center, Biologics, Inc., as described in the drug distribution center's SOPs.

All drug is received in dry dock and then sent to the DFCI Pharmacy. Once the packages are opened the packing slip is examined. Proper documentation of the Janssen specific protocol number is required on the packing slips. The pharmacy technicians identify the received drug as investigational and the drug is transferred to the investigational pharmacy for receipt and acknowledgement. Investigational drug is stored according to the DFCI protocol number in research refrigerators, separated from non-research material.

Each individual sub-site will be allowed to utilize their local SOP for investigational product once the SOP is reviewed by the coordinating center for compliance with GCP and ICH guidelines.

3.4 Temperature excursions

Biologics, Inc. should follow their standard of practice as well as the guidance from the protocol document regarding temperature excursions.

DFCI pharmacy refrigerators record temperatures continuously and are attached to an alarm for any excursion. If an excursion happens after hours a pharmacist is on call to answer the alarm. Investigational product is then quarantined according to the requirements per protocol.
Each individual sub-site should follow their local standard of practice as well as the guidance from the protocol

document regarding temperature excursions. The coordinating center will review each SOP to ensure that it complies with GCP and ICH guidelines.

Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). Do not freeze or shake. Protect from light. This product contains no preservative. If the storage temperature falls outside of the range accepted in the institutional SOP, this is considered a temperature excursion. When a temperature excursion occurs, each individual sub-site must quarantine the product and inform the coordinating center as soon as possible. The coordinating center is responsible for liaising with Janssen Scientific Affairs, LLC for guidance on continued use of the product and will inform sites whether the product is suitable for continued use.

4. IP Accountability

4.1 IP use in accordance with this IIS

Biologics, Inc. will include pertinent information on all packing slips and include auxiliary documents to inform sites of instructions for use. In all communications with the sites prior to shipment, the drug distribution center can review this information with the receiver

Each supply of investigational product will come equipped with a packing slip from Janssen Scientific Affairs, LLC. This packing slip will have the Janssen Scientific Affairs, LLC study number. Each participating site will be informed during the site initiation visit that investigational product should only be used for the IIS.

4.2 Process for maintaining IP transaction logs

All participating sites are required to maintain adequate accountability and storage of investigational agents. As outlined in the study protocol and study data safety monitoring plan.

5. IP Destruction

5.1 Confirmation of each site's SOP to destroy IP at site

Because of their participation in studies using DFCI-supplied investigational drug, all DFCI institutions have the capability of either destroying Study Product at their site or have an SOP for return of the Study Product to the distributor for destruction.

5.2 Confirmation that documentation of each site's SOP for IP destruction will be retained

A copy of the sub-site drug destruction SOP will be filed in the Trial Master File.

5.3 Confirmation that each site will retain documentation of IP destruction

Drug destruction and/or pharmacy records will be kept current reviewed during routine monitoring visits and prior to study closeout at all participating sites, as outlined in the study protocol and study data safety monitoring plan.

6. IP Distribution

6.1 Shipping information contacts at S-I site or at drug distribution supplier for sites participating in the IIS

Biologics, Inc. and the coordinating center will provide drug ordering instructions to all participating sites.

Biologics, Inc. contact details for drug ordering:
Fax: 919-256-0794
Email: CRSOrders@biologicsinc.com

Throughout the course of the study, a clinical hotline support, staffed with clinical pharmacists, is made available 24/7/365 in the event an investigator or site coordinator has a question.
Hotline phone: 1-800-693-4906

During the approval and activation process, the coordinating center will inform Janssen Scientific Affairs, LLC and the drug distribution center of any new site prior to activation of said site and prior to any IP shipment to said site.

6.2 Confirmation that all necessary documents are in place prior to shipment to any participating site

Biologics, Inc. and DFCI will execute a contract prior to study launch. DFCI will execute any agreements required with the sub-sites prior to the activation of said site. DFCI has existing process in place for confirmation of local IRB review prior to patient registration. Each site will be unable to request shipment until IRB approval centrally at the coordinating center is received and all regulatory documents (e.g. CVs, MLs, DOA, etc.) have been filed in the Trial Master File.

6.3 Distribution/coordination plan for shipping IP to participating sites

In general, a minimum of a three-month forecasted supply of study drug will be shipped to each participating site to ensure that drug shipments do not occur more frequently than once a quarter to each site. Exceptions to this rule of thumb should be reviewed with DFCI.

6.4 Confirmation that S-I or IP distribution supplier will record and maintain shipping documentation of IP to participating sites

Biologics, Inc. will record a complete accountability record including date of dispense, site name, quantity dispensed, and balance forward will be recorded. Study accountability records are documented in electronic 21CFR format and are kept in a secured area for the duration of the study.

Each individual sub-site will maintain a record of shipment according to their local SOPs for maintaining documentation of IP shipment. This SOP will be reviewed by the coordinating center for compliance with GCP and ICH guidelines.

7. Packaging and Labeling

7.1 IP should be clearly identified to be used only for the specified IIS

Biologics, Inc. will include a disclaimer that IP is to be used only for the specified IIS on the packing slip, or on auxiliary documentation that is placed on the study product prior to dispense to the study site.

Janssen Scientific Affairs, LLC will include the Janssen protocol number clearly on the packing slip or auxiliary documentation in the shipment of study drug to Biologics Inc.

The coordinating center will ensure a yearly monitoring review of pharmacy drug accountability records. The drug accountability record and the drug destruction log will be collected at the end of the study per DFCI SOPs.

7.2 Any additional participating sites' labeling requirements per institution's policy/SOP and/or local and/or country regulations

Biologics, Inc. will create, submit, and agree upon the shipping label with DFCI prior to study launch and any requirements at specific study sites will need to be discussed during this process. Shipping and handling from the drug distribution vendor to each site will follow the drug distribution vendor's standards of practice. The practices will meet all GCP and ICH guidelines as appropriate.

APPENDIX F: RAPID DARATUMUMAB INFUSION GUIDELINE

Standard daratumumab infusion

Cycle 1, days 1 and 8:
The first infusion of daratumumab should be prepared in a total volume of 1000 mL. After the first infusion, if no infusion reactions were experienced during the first 3 hours, the medication may be prepared using a total volume of 500 mL going forward. The initial rate of administration is 50 mL/hr. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 ml/hour increments every 60 minutes to a maximum of 200 mL/hr.

Subsequent infusions:
The initial rate of administration can be increased to 100 mL/hr if there were no grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mL/hour increments every 60 minutes to a maximum of 200 mL/hr.

Standard premedication regimen:

	First and Second Infusions	Subsequent Infusions
Pre-infusion (~1 hour before start of infusion)	• diphenhydramine 25- 50 mg IV /PO • acetaminophen 975 mg PO • methylprednisolone 100 mg IV • famotidine 20 mg IV* • montelukast 10 mg PO* • fexofenadine 60 mg PO*	• diphenhydramine 25- 50 mg IV/PO • acetaminophen 975 mg PO • methylprednisolone 60mg mg IV
Peri-infusion (~2 hours after start of infusion)	• diphenhydramine 25 mg IV* • famotidine 20mg IV* • methylprednisolone 40 mg IV*	
Post infusion	• oral steroid (methylprednisolone 20 mg or equivalent) Days 2-3 after infusion (24 and 48 hours after the completion daratumumab).	• oral steroid (methylprednisolone 20 mg or equivalent) Days 2-3 after infusion (24 and 48 hours after the completion daratumumab).

* If after completion of cycle 2 and no infusion reactions were experienced or if approved by the treating investigator, the 24-48 post infusion steroid may be waived if clinically appropriate

Cycle 2 and Subsequent Rapid Infusion:
For patients who tolerate Cycle 1 Day 22 without any grade (grade 1 or greater) hypersensitivity reaction, subsequent daratumumab infusions can be administered at an initial rate of 20% of the total dose over 30 minutes, followed by the remaining 80% of the total dose over 60 minutes (90-minute total infusion time).

- Rapid infusion will be given in a total volume of 500 mL

- This allows for a rate of 200 mL/hr for the first 30 minutes and a rate of 400 mL/hr for the final 60 minutes.
- If a patient experiences any grade hypersensitivity reaction during standard infusion rate, the patient is not eligible for rapid infusion until they have received standard infusion daratumumab for two subsequent infusions without any grade hypersensitivity reaction.
- If during a rapid infusion, the patient experiences an infusion reaction of any grade, the patient is not eligible to receive additional rapid infusions until they have received standard infusion daratumumab without any grade hypersensitivity reaction
- Please see table below for hypersensitivity reaction grading criteria

Grading of Infusion Related Reactions NCI CTCAE v5.0					
Grade	1	2	3	4	5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for </= 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

Clinical Trial Experience: Barr H, Dempsey J, Waller A, et al. Ninety-Minute Daratumumab Infusion Is Safe in Multiple Myeloma. Blood 2017 130: 1889.

<u>*Background*</u>*:* Daratumumab, an anti-CD38 monoclonal antibody, was first approved for the treatment of relapsed and refractory multiple myeloma (MM) in November of 2015. The approved initial infusion lasts at least 6.5 hours, second infusion for 4.5 hours and all subsequent infusions over 3.5 hours. The risk of infusion related reactions (IRRs) is very low after the second infusion, and the prolonged continued infusion time results in long days for patients. Because of our success infusing other monoclonal antibodies over shorter times, such as rituximab, we hypothesized that shortening the daratumumab infusion from 3.5 hours to 90 minutes beginning with the third infusion would not increase the incidence of IRRs.

<u>*Methods*</u>*:* This is a single-center safety study of an accelerated daratumumab infusion in patients receiving standard of care daratumumab therapy. Patients were eligible once they received at least 2 prior doses of

daratumumab, administered per standard prescribing information. Previous IRR was not an exclusion criterion. The accelerated infusion was calculated to deliver 20% of the dose over the first 30 minutes, then the remaining 80% over 60 minutes, resulting in an estimated 90-minute infusion. Patients who tolerated the infusion well were allowed to continue the accelerated rate. Premedication regimens were allowed to be altered based on previous tolerability. Simon's two-stage optimal design was utilized to design the study based on the incidence of grade 3 or above IRR. With 80% power the design allows 7 patients to be treated in the first stage, and if no patients experienced ≥ grade 3 IRR, an additional 21 patients would be treated. Out of all 28 patients, if 2 or more experienced ≥ grade 3 IRR, the regimen would be declared as too toxic. The protocol was approved by the cancer institutional review board.

Results: Twenty-eight patients were treated with daratumumab utilizing the accelerated rate, 8 of which received the accelerated infusion with their third dose of daratumumab. The premedication regimen varied patient-to-patient and did not impact tolerability of the accelerated infusion. There were 5 patients who did not receive any steroid premedication and 3 who received reduced doses (< 12 mg) of dexamethasone. Of the 28 patients treated, there was only 1 adverse reaction - a grade 2 hypertension during which the infusion was paused for a patient that had received 10 prior infusions at standard rates. The patient received a diuretic, the infusion was resumed and subsequently increased to the accelerated rate without further incidence of hypertension. There were no grade 3 or higher IRRs. At the 4-week follow-up, all patients remaining on daratumumab treatment continued at the accelerated infusion rate.

Conclusion: An accelerated infusion rate of daratumumab delivering 20% of the dose over 30 minutes and 80% over 60 minutes is feasible and well-tolerated in patients who have received 2 prior doses of daratumumab at standard infusion rates. Starting with the third dose of daratumumab therapy, the 90-minute infusion is now standard practice at our institution.

References:

1. Barr H, Demspey J, Waller A, et al. Ninety-minute daratumumab infusion is safe in multiple myeloma. Leukemia. 31 March 2018; 1476-5551

APPENDIX G: SUBJECT SAFETY CARD

Patient ID Card for Clinical Trial

DFCI 17-212

Please always carry this card with you and share with all your healthcare providers

Site Number: _____

Subject's Number: _____

I am participating in a clinical study being supported by Janssen Scientific Affairs, LLC. As part of this study, I am taking the following medication:
Daratumumab (marketed as DARZALEX), an Investigational Medicinal Product

1 of 4

In case of emergency, or if you find this card, please contact the doctor listed below:

Study Doctor's Name/Hospital:

_____

24-Hour Emergency Telephone:

_____

If you are unable to reach the study doctor in the event of an emergency, please contact the study supporter at:
24-Hour Emergency Telephone:
1-866-447-2701

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DARATUMUMAB PATIENTS: Provide this card to health care providers BEFORE blood transfusion

Indirect antiglobulin test (IAT) also known as an Indirect Coombs test (antibody screen and crossmatch) will show positive results in patients taking daratumumab.
This phenomenon and the methodology to correct a positive IAT is described in the publication in the journal Transfusion: *http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf*

You may also call the doctor listed on this card for more information.

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Before I started taking daratumumab
my test results collected on
(insert date dd-mmm-yyyy)_____were:

Blood type: □ A □ B □ AB □ O □ Rh+ □ Rh-

Indirect antiglobulin test (antibody screen) was:
□ Negative
□ Positive for the following antibodies: _____

Patient ID card, v1.0, 19-Jul-2016

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