Protocol Title:

Phase II Trial of Combination of Ixazomib and Lenalidomide and Dexamethasone in Smoldering Multiple Myeloma

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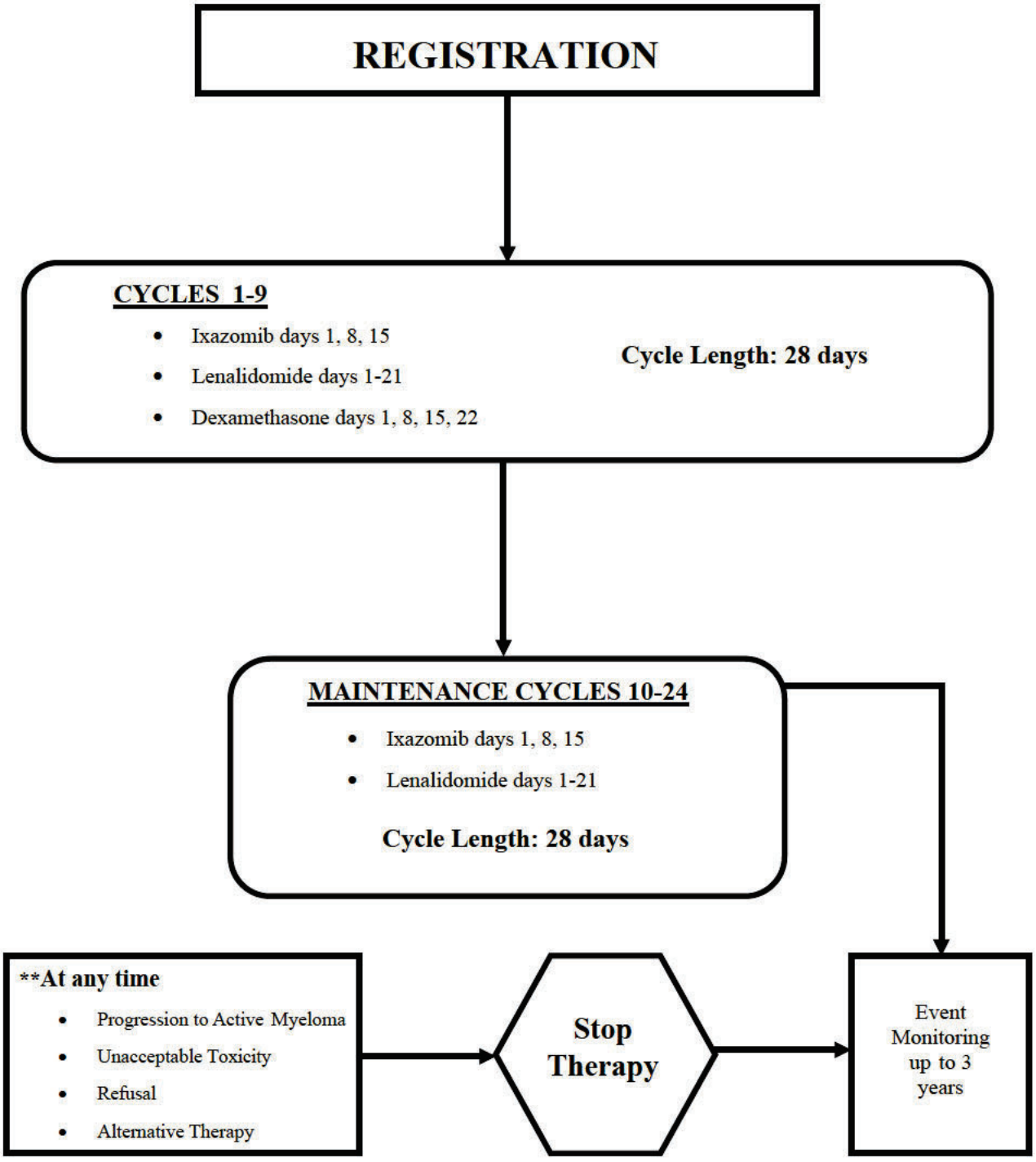
SCHEMA



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

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

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

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

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

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

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

PROTOCOL SUMMARY

Study Title: Phase II Trial of Combination of Ixazomib and Lenalidomide and Dexamethasone in Smoldering Multiple Myeloma

Phase: II

Number of Patients: 56

Study Objectives:

Primary Objectives

- To determine the proportion of patients with high-risk smoldering multiple myeloma patients who are progression free at 2 years after receiving IRD combination therapy

Secondary Objectives

- To assess the response rate of the combination in these patients
- To assess duration of response
- To assess safety of the combination
- To examine molecular evolution of the tumor cells
- To determine minimal residual disease (MRD)
- To assess time to progression and progression free survival

Overview of Study Design:

This is a single arm phase II study using the combination of Ixazomib and lenalidomide + dexamethasone in patients with high-risk smoldering multiple myeloma. The study is designed to examine novel therapeutic combinations in patients with smoldering MM. Based on the activity of lenalidomide and dexamethasone in patients with SMM and based on the safety and activity profile of Ixazomib/len/dex in patients with untreated MM, we propose to examine in a phase II trial the activity of ixazomib/lenalidomide/dexamethasone (IRD) in patients with high-risk smoldering MM.

Study Population:

SELECT INCLUSION CRITERIA

- Age ≥ 18 years.
- High-risk smoldering myeloma based on the new Rajkumar et al criteria for high-risk disease[1].
- No evidence of CRAB criteria or new criteria of overt MM which includes the following:
    - 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)
    - No evidence of the following new criteria for active MM including the following: Bone marrow plasma cells >60%, Serum involved/uninvolved FLC

ratio ≥100 (light chain smoldering MM is allowed), and MRI with more than one focal lesion.

- ECOG Performance Status (PS) 0, 1, or 2.
- The following laboratory values obtained ≤ 21 days prior to registration:
  - ANC ≥ 1000/μL
  - PLT ≥ 75,000/μL
  - Total bilirubin ≤ 1.5 mg/dL (If total is elevated check direct and if normal patient is eligible.)
  - AST ≤ 3 x institutional upper limit of normal (ULN)
  - ALT ≤ 3 x institutional upper limit of normal (ULN)
  - Calculated creatinine clearance ≥ 30 mL/min

SELECT EXCLUSION CRITERIA

- Symptomatic Multiple Myeloma or any evidence of CRAB criteria. Any prior therapy for Multiple Myeloma should also be excluded. Bisphosphonates are not excluded
- Other concurrent chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered investigational. Prior therapy with bisphosphonate is allowed. Prior radiation therapy to a solitary plasmacytoma is allowed.

Duration of Study: 5 years

1. OBJECTIVES

Smoldering Multiple Myeloma (SMM) is a heterogeneous disease entity that includes patients who have a disease burden that is higher than that in patients with MGUS but who are not yet symptomatic[2]. The term SMM was first described by Greipp and Kyle et al in 1980[3] and was followed by many other descriptions terming it indolent MM[4], or Durie Salmon Stage I[5]. 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[6,7]. 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[2].

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% [8]; an abnormal FLC-ratio ≥ 100 (involved kappa) or < 0.01 (involved lambda) [9]: and/or 2 or more focal bone marrow lesions detected by functional imaging including PET-CT and/or MRI [10,11]. 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[12]. The most common factors used to stratify patients with SMM are the Mayo Clinic criteria[12,13] and the Spanish PETHEMA criteria[14]. 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)[12,13], 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[12,13]. 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[14].

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)[15-17]. 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[18]. Therefore, there is a need to examine novel therapeutic combinations in patients with high-risk smoldering MM. Based on the activity of lenalidomide and dexamethasone in patients with high-risk SMM and based on the safety and activity profile of Ixazomib and lenalidomide in patients with relapsed MM[19-22], we propose to examine the activity of Ixazomib, lenalidomide, and dexamethasone in patients with SMM.

Our overarching hypothesis is that early therapeutic interventions in patients with smoldering MM will prevent/delay progression to overt MM. We will examine the *in vivo* activity and safety of Ixazomib, lenalidomide, and dexamethasone in patients with high-risk SMM.

1.1 Study Design

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

1.2 Overview of Study Design

This is a single arm phase II study using the combination of Ixazomib and lenalidomide + dexamethasone in patients with high-risk smoldering multiple myeloma.

The study is designed to examine novel therapeutic combinations in patients with smoldering MM. Based on the activity of lenalidomide and dexamethasone in patients with SMM and based on the safety and activity profile of Ixazomib/len/dex in patients with untreated MM, we propose to examine in a phase II trial the activity of ixazomib/lenalidomide/dexamethasone (IRD) in patients with high-risk smoldering MM, including those with all risk factors of SMM.

1.3 Number of Patients

A total of 56 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.

1.4 Duration of Study

A treatment cycle is defined as 28 consecutive days.

Patients will receive 9 cycles of induction therapy followed by 15 cycles of maintenance therapy for a total of 24 months.

For treatment cycles 1 and 2, a +/- 3 day window is allowed. For treatment cycles 3 through 24, a +/-7 day window is allowed. Treatment plan is designed to be administered on an outpatient basis, however if necessary, may be given as inpatient.

1.5 Primary Objectives

- To determine the proportion of high-risk smoldering multiple myeloma patients who are progression free (free of symptomatic Myeloma defining events) at 2 years after receiving Ixazomib and lenalidomide + dexamethasone combination therapy

1.6 Secondary Objectives

- To assess the response rate of the combination in these patients
- To assess time to progression and progression free survival
- To assess duration of response
- To assess safety of the combination
- To examine molecular evolution of the tumor cells obtained

- To determine minimal residual disease (MRD)

2. BACKGROUND

2.1 Multiple Myeloma

Multiple myeloma is a plasma cell neoplasm characterized by multifocal proliferation of clonal, long-lived plasma cells associated with an overproduction of monoclonal gammaglobulin [23]. In 2010 the International Myeloma Working Group (IMWG) defined monoclonal gammopathy of undetermined significance (MGUS) by the presence of serum M-protein < 3g/dL, clonal plasma cell population in the bone marrow < 10%, and the absence of end-organ damage such as hypercalcemia (serum calcium ≥ 11.5 mg/dL), renal insufficiency (serum creatinine ≥ 2 mg/dL), anemia (hemoglobin value below the lower limit of normal by more than 2 g/dL or hemoglobin value < 10 g/dL) and lytic bone lesions (CRAB features) that can be attributed to the plasma cell proliferative disorder [24]. Smoldering multiple myeloma was defined by the presence of serum M-protein ≥ 3 g/dL or IgA> 2g/ dL or urinary monoclonal protein > 500 mg/ dL and/or clonal bone marrow plasma cells ≥ 10% and the absence of CRAB features clinically.

In a large population based study in Olmsted County, MN, Kyle et al. analyzed serum samples of more than 75% of residents, 50 years or older, within the county [25]. 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%) [26]. 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 [12,13]. 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.[8]

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

Model	No. of Risk Factors	5-Year Progression %	Time to Progression (in years)
Mayo Clinic Model Risk Factors: • M-protein ≥ 3.0g/dL • ≥10% plasma cells in the BM • FLC ratio outside the range of 0.125 to 8	1	25	10
	2	51	5.1
	3	76	1.9

2.2 MGUS and SMM consistently precedes multiple myeloma

Since the early description of monoclonal gammopathy of undermined significance it was known that some cases of MGUS progressed to symptomatic myeloma but it was not clear whether all cases of myeloma are preceded by MGUS. In a study of more than 77,000 individuals, 55 to 74 years of age, from a cancer screening trial, Landgren et al found 71 patients who developed multiple myeloma[27]. 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 [28].

2.3 Molecular studies in MGUS and SMM

A recent study using SNP-based arrays compared MGUS, SMM and MM samples [29]. They found copy number abnormalities in all stages. The incidence of genomic imbalance did increase from a median of 5/case for MGUS to 7.5/case for SMM and 12/case for MM. The study also noted certain genomic changes that were exclusive to MM including 11q and 21q gains and 16q and 22q deletions. Interestingly, the study found these abnormalities in a small subclone in MGUS patients indicating that most if not all of the chromosomal changes may be already present at the MGUS state. These findings also support a possible role of 'clonal tides' in the evolution from precursor state to symptomatic myeloma as explained below.

Two major pathways have been proposed as the early oncogenic events in the development of the myeloma cell based on chromosomal abnormalities noted in MGUS, SMM and MM- the non-hyperdiploid and the hyperdiploid pathway. The main cytogenetic changes that have been observed in MGUS and SMM are indicated in the table below.

Table 2: Cytogenetic abnormalities in MGUS, SMM and MM

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

Other molecular studies in MGUS and SMM included microRNA studies. MicroRNAs are single stranded RNA molecules that regulate gene expression posttranscriptionally and are being implicated in a large number of cancers [30]. 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 [31]. 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 [30,31]. The mir17 cluster has been shown to upregulated by the transcription factor c-Myc, which is considered a late event in myeloma progression [32-34].

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 [35]. 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[36-40]. 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[29,41,42].

2.4 Definition of SMM

The diagnosis of smoldering (asymptomatic) multiple myeloma (SMM) is based on [43,44]:

- Serum monoclonal protein (IgG or IgA) ≥ 3.0 g/dL or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 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 [43,44]

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*
- MRI with two or more focal lesion that is at least 5 mm or greater in size

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

2.5 Definitions of High-Risk SMM

Based on the new defined high-risk criteria for smoldering myeloma based on [1] as described in table 3 below:

Table 3 Bone marrow clonal plasma cells ≥10% and any one or more of the following:
Serum M protein ≥ 3.0g/dL
IgA SMM
Immunoparesis with reduction of two uninvolved immunoglobulin isotypes
Serum involved/uninvolved free light chain ratio ≥8 (but less than 100)
Progressive increase in M protein level (Evolving type of SMM)†
Bone marrow clonal plasma cells 50–60%
Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes
t (4;14) or del 17p or 1q gain
Increased circulating plasma cells
MRI with diffuse abnormalities or 1 focal lesion
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction
Monoclonal light chain excretion of 500mg/24 hours or higher*

† Increase in serum monoclonal protein by ≥10% on two successive evaluations within a 6 month period
* Monoclonal Light Chain Smoldering

2.6 Treatment of High-Risk SMM

In a randomized open-label phase 3 trial [18], 119 patients with high-risk smoldering myeloma were randomized to treatment or observation. Patients in the treatment group received an induction regimen (lenalidomide at a dose of 25 mg per day on days 1 to 21, plus dexamethasone at a dose of 20 mg per day on days 1 to 4 and days 12 to 15, at 4-week intervals for nine cycles), followed by a maintenance regimen (lenalidomide at a dose of 10 mg per day on days 1 to 21 of each 28-day cycle for 2 years). The primary end point was time to progression to symptomatic disease. Secondary end points were response rate, overall survival, and safety. After a median follow-up of 40 months, the median time to progression was significantly longer in the treatment group than in the observation group (median not reached vs. 21 months; hazard ratio for progression, 0.18; 95% confidence interval [CI], 0.09 to 0.32; $P < 0.001$). The 3-year survival rate was also higher in

the treatment group (94% vs. 80%; hazard ratio for death, 0.31; 95% CI, 0.10 to 0.91; P=0.03). A partial response or better was achieved in 79% of patients in the treatment group after the induction phase and in 90% during the maintenance phase. Toxic effects were mainly grade 2 or lower. Early treatment for patients with high-risk smoldering myeloma delays progression to active disease and increases overall survival. (NCT00480363).

2.7 Ixazomib (MLN9708)

2.7.1 Preclinical Experience

Please refer to the current ixazomib Investigator's Brochure (IB) and Safety Management Attachment (SMA).

2.7.2 Clinical Experience

Ixazomib has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapse/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent ixazomib and ixazomib in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, 2 phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with Lenalidomide and Dexamethasone (LenDex) versus placebo/LenDex. Both trials are combining ixazomib at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. Studies evaluating the safety and pharmacokinetic (PK) of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of NDMM are ongoing.

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per

protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (*n* = 201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

A recent study was published showing that IRD is highly effective in newly diagnosed MM [45]. The study enrolled patients newly diagnosed with multiple myeloma aged 18 years or older with measurable disease, Eastern Cooperative Oncology Group performance status 0-2, and no grade 2 or higher peripheral neuropathy, and treated them with oral ixazomib (days 1, 8, 15) plus lenalidomide 25 mg (days 1-21) and dexamethasone 40 mg (days 1, 8, 15, 22) for up to 12 28-day cycles, followed by maintenance therapy with ixazomib alone. In phase 1, patients received escalating doses of ixazomib (1.68-3.95 mg/m(2)) to establish the recommended dose for phase 2. The primary endpoints were maximum tolerated dose for phase 1, and the rate of very good partial response or better for phase 2. Safety analyses were done in all patients who received at least one dose of study drug; efficacy analyses were done in all patients who received at least one dose of study drug at the phase 2 dose, had measurable disease at baseline, and had at least one post-baseline response assessment. This study is registered at ClinicalTrials.gov, number NCT01217957. FINDINGS: Between Nov 22, 2010, and Feb 28, 2012, the study enrolled 65 patients (15 to phase 1 and 50 to phase 2). Four dose-limiting toxic events were noted in phase 1: one at a dose of ixazomib of 2.97 mg/m(2) and three at 3.95 mg/m(2). The maximum tolerated dose of ixazomib was established as 2.97 mg/m(2) and the recommended phase 2 dose was 2.23 mg/m(2), which was converted to a 4.0 mg fixed dose based on population pharmacokinetic results. Grade 3 or higher adverse events related to any drug were reported in 41 (63%) patients, including skin and subcutaneous tissue disorders (11 patients, 17%), neutropenia (eight patients, 12%), and thrombocytopenia (five patients, 8%); drug-related peripheral neuropathy of grade 3 or higher occurred in four (6%) patients. Five patients discontinued because of adverse events. In 64 response-evaluable patients, 37 (58%, 95% CI 45-70) had a very good partial response or better. INTERPRETATION: The all-oral combination of weekly ixazomib plus lenalidomide and dexamethasone was generally well tolerated and appeared active in newly diagnosed multiple myeloma. Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

2.8 Pharmacokinetics and Drug Metabolism

Clinical IV and PO PK data show that ixazomib citrate (measured as the biologically active boronic acid form of ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib citrate is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) concentration (Tmax) of approximately 0.5 to 2.0 hours and a terminal disposition half-life (t1/2) after multiple dosing of approximately 5 to 7 days [1]. Results of a population PK analysis (n = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA [2]. Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for ixazomib using the population PK analysis. Please refer to the current ixazomib IB and Safety Management Attachment (SMA) for information on the PK for IV doses of ixazomib.

Metabolism appears to be the major route of elimination for ixazomib, and urinary excretion of the parent drug is negligible (< 5% of dose). In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450s (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes was 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). Ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4 nor a time-dependent inhibitor of CYP3A4/5. The potential for ixazomib treatment to produce drug-drug interactions (DDIs) via CYP inhibition is inferred to be low. However, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor or inducer because of the potential for first-pass metabolism when ixazomib is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of ixazomib in human liver microsomes. Ixazomib may be a weak substrate of P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of Pgp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of Pgp, BCRP, and MRP2 is, therefore, inferred to be low. Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

Further details on these studies are provided in the IB.

Table 4	Clinical Studies of Oral Ixazomib	
Trial/ Population	**Description**	**Doses Investigated**
C16003 RRMM N = 60	PO, TW, single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23mg/m^2) Closed to enrollment
C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5-mg fixed dose[a] W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose[a] W MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5-mg fixed dose[a] W

Table 4	Clinical Studies of Oral Ixazomib	
Trial/ Population	**Description**	**Doses Investigated**
C16010 RRMM N = 200	PO, W, with LenDex versus placebo-LenDex	4.0 mg W
C16011 RRAL N = 4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg W
C16013 RRMM N = 9	PO, W, with LenDex	4.0 mg W
C16014 Symptomatic MM N=701	PO, combination with LenDex	ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22
C16015 Symptomatic MM with normal renal function or severe renal impairment N=28	PO, combination with Dex	Part A: ixazomib 3.0 mg on Day 1 Part B: ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle

Table 4	Clinical Studies of Oral Ixazomib	
Trial/ Population	**Description**	**Doses Investigated**
C16017 RR follicular lymphoma N=58	PO, W	4.0, 5.3, and 7.0 mg, W Treatment at RP2D once determined.
C16018 Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=45	**Part A:** PO, Day 1 of 15-day cycle **Part B:** PO, W	1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)
TB-MC010034 RRMM N = 10	PO, W	4.0 mg, W Single agent: 4.0 mg Combination with Rd

Abbreviations: RRAL = Relapsed and/or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area; Dex=dexamethasone; DLT = dose-limiting toxicity; IV = intravenously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RR= relapsed and/or refractory; RRAL= relapsed and/or refractory systemic light chain amyloidosis RRMM = relapsed and/or refractory multiple myeloma; TBD = to be determined; TW = twice weekly; W = weekly; RP2D= recommended phase 2 dose.

Note that blinded data from pivotal Studies C16010 and C16011 are not included.

a Approximate BSA and fixed dosing equivalence: 3 mg~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg~ equivalent to 2.97 mg/m^2 BSA dosing.

2.9 Clinical Trial Experience Using the Oral Formulation of Ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma) have been treated in studies evaluating the oral ixazomib formulation. These patients have been treated with different doses of ixazomib either as a single-agent treatment (in 201 patients) or in combination with currently clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 4.

Overview of the Oral Formulation of Ixazomib

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients have been treated with different doses of ixazomib as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib studies (C16003, C16004, C16007, and C16009) are shown in Table 5.

Table 5 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class **Preferred Term**	**Oral Single Agent** **Total** **n = 201** **n (%)**
Subjects with at Least One Adverse Event	197 (98)
Gastrointestinal disorders	160 (80)
Nausea	106 (53)
Diarrhoea	88 (44)
Vomiting	77 (38)
Constipation	46 (23)
Abdominal pain	33 (16)
General disorders and administration site conditions	151 (75)
Fatigue	103 (51)
Pyrexia	51 (25)
Oedema peripheral	27 (13)
Asthenia	31 (15)
Nervous system disorders	92 (46)
Headache	29 (14)
Dizziness	26 (13)
Neuropathy peripheral	21 (10)
Metabolism and nutrition disorders	107 (53)
Decreased appetite	64 (32)

Table 5 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class **Preferred Term**	**Oral Single Agent** **Total** **n = 201** **n (%)**
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)
Anaemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)
Rash macular[a]	23 (11)
Musculoskeletal and connective tissue disorders	93 (46)
Back pain	24 (12)
Arthralgia	28 (14)
Respiratory, thoracic and mediastinal disorders	78 (39)
Cough	28 (14)
Dyspnoea	30 (15)
Infections and infestations	89 (44)
Upper respiratory tract infection	31 (15)

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

a. Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

As of 27 March 2013, there are 5 studies actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens.

The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 4). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

Table 6 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class **Preferred Term**	**Total Oral Combo Agent (5/6/8/13)** ***n* = 173** **n (%)**
Subjects with at Least One Adverse Event	163 (94)
Gastrointestinal disorders	139 (80)
Nausea	65 (38)
Diarrhoea	81 (47)
Vomiting	51 (29)
Constipation	57 (33)
General disorders and administration site conditions	132 (76)
Fatigue	76 (44)
Pyrexia	39 (23)
Oedema peripheral	61 (35)
Asthenia	20 (12)
Nervous system disorders	115 (66)
Headache	28 (16)
Dizziness	34 (20)
Neuropathy peripheral	45 (26)
Metabolism and nutrition disorders	91 (53)
Decreased appetite	25 (14)
Hypokalaemia	34 (20)
Blood and lymphatic system disorders	88 (51)
Thrombocytopenia	49 (28)
Anaemia	45 (26)
Neutropenia	43 (25)
Lymphopenia	20 (12)
Skin and subcutaneous tissue disorders	102 (59)
Rash maculopapular[a]	29 (17)
Rash macular[a]	22 (13)
Musculoskeletal and connective tissue disorders	99 (57)
Back pain	42 (24)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)

Table 6 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class **Preferred Term**	**Total Oral Combo Agent (5/6/8/13)** ***n* = 173** **n (%)**
Cough	36 (21)
Dyspnoea	26 (15)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors, non-Hodgkin's disease, Hodgkin's disease, relapsed and/or refractory multiple myeloma [RRMM, relapsed or refractory systemic light chain amyloidosis [RRAL], and newly diagnosed multiple myeloma [NDMM] [45]to date[46].

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of ixazomib.

2.10 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involves 2 studies (C16003 and C16004) with similar objectives, but each investigated 1 of the 2 dosing schedules commonly used with the first-in-class proteasome inhibitor, VELCADE.

Study C16003 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM[47]. Study C16004 is an open-label, dose escalation, phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with RRMM[48]. Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

In the dose escalation component of both studies, patients had multiple myeloma that had relapsed following at least 2 lines of therapy that must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, when the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were to be enrolled into 1 of 4 expansion cohorts, including a relapsed and refractory cohort, a carfilzomib cohort, a proteasome inhibitor-naïve cohort, and a VELCADE-relapsed cohort.

Final study results are currently being analyzed, but preliminary data suggest that ixazomib has anti-tumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated. Please refer to the ixazomib IB and SMA for further information.

2.11 Newly Diagnosed Multiple Myeloma (NDMM)

Multiple research paths are being explored in patients with NDMM with a focus on evaluating ixazomib in combination with agents commonly used across treatment settings. The development of ixazomib in combination with lenalidomide with dexamethasone (LenDex) in patients with NDMM who are transplant eligible or ineligible involves 2 studies (C16005 and C16008) with similar study designs except for a few key differences, namely the schedules of ixazomib and dexamethasone[45]. Ixazomib is also being evaluated in combination with melphalan and prednisone (MP) for patients who are not transplant eligible due to age or coexisting morbidity (in Study C16006).

All 3 studies are phase 1/2, with phase 1 focusing on safety and phase 2 on efficacy (and further characterization of safety). Please refer to the ixazomib IB and SMA for further information.

2.12 Clinical Trial Experience Using the Intravenous Formulation of Ixazomib

See the IB for descriptions of the 2 studies that investigated IV ixazomib in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

2.13 Trial Rationale

Based on the activity of lenalidomide and dexamethasone in patients with SMM and based on the safety and activity profile of Ixazomib/len/dex in patients with untreated MM (ASH 2014), we propose to examine in a phase II trial the activity of ixazomib/lenalidomide/dexamethasone (IRD) in patients with high-risk smoldering MM.

Patients who develop symptomatic disease will receive induction therapy with standard therapeutic options for multiple myeloma including combinations such as those of proteasome inhibitors, immunomodulators and steroids or cyclophosphamide, proteasome inhibitors and dexamethasone.

Patients who are eligible for stem cell collection will have the option to collect stem cells during the course of therapy on this trial at the time of best response (CR or VGPR) or after 9 cycles of induction therapy. If we observe any problems with stem cell collection, we will follow the current standard guidelines of using cyclophosphamide or plerixafor mobilization. Based on data using combination therapies for induction, there has been no major concerns regarding stem cell collections after treatment with those agents.

2.14 Potential Risks and Benefits

Please refer to the current ixazomib IB and SMA.

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Millennium. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports expanded development of ixazomib for the treatment of patients with advanced malignancy. This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2.15 Correlative Studies Background

2.15.1 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[49,50]. The genomic complexity in MM was recently corroborated by massive parallel-sequencing studies displaying the lack of a universal driving mutation[35]. Recent studies have shown intraclonal heterogeneity that occurs at different stages of progression in MM[36,37]. 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[51,52]. 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[34]. 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 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)[35,36]. 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.

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[35,56]. 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]. All bioinformatics analysis will be performed by Dr. Shi and Michor, who are expert Bioinformaticians and have analyzed the data shown in the preliminary data.

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].

Single-cell sequencing of the tumor microenvironment. Investigators at the Broad Institute and Harvard Medical School have recently developed the technology of droplet sequencing (Drop-seq). In addition, multiple publications have shown that that single-cell RNA sequencing (RNA-seq) of the tumor microenvironment can define genotypic and phenotypic states of tumor cells and surrounding microenvironment, and that the microenvironment affected the gene expression program of tumor cells and their resistance to therapy. We will apply similar techniques in this study to evaluate the tumor microenvironment and assess specific changes in cell type and transcriptional signature of BM niche cells that correlate with tumor progression or resistance to therapy.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Age ≥ 18 years.

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

Definition of high-risk SMM:

- Bone marrow clonal plasma cells ≥ 10% and ≤ 60% and any one or more of the following:
  - Serum M protein ≥3.0g/dL (IgA, IgG, IgM, or IgD)
  - IgA SMM
  - Immunoparesis with reduction of two uninvolved immunoglobulin isotypes
  - Serum involved/uninvolved free light chain ratio ≥8 (but less than 100)
    - Free Light Chain Smoldering Myeloma patients as defined in section 2.4 are not excluded
  - Progressive increase in M protein level (Evolving type of SMM)
    - Increase in serum monoclonal protein by ≥10% on two successive evaluations within a 6-month period
  - Bone marrow clonal plasma cells 50-60%
  - Abnormal plasma cell immunophenotype (≥ 95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes
  - t (4;14) or del 17p or 1q gain
  - Increased circulating plasma cells
  - MRI with diffuse abnormalities or 1 focal lesion
  - PET-CT with one focal lesion with increased uptake without underlying osteolytic bone destruction
  - Urine monoclonal light chain excretion ≥500 mg/24 hours

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

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

- ANC ≥ 1000/μL
- PLT ≥ 75,000/μL. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
- Total bilirubin ≤ 1.5 mg/dL (If total is elevated check direct and if normal patient is eligible.)
- AST ≤ 3 x institutional upper limit of normal (ULN)
- ALT ≤ 3 x institutional upper limit of normal (ULN)

- Calculated creatinine clearance ≥ 30 mL/min

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

3.1.6 Female patients who are postmenopausal for at least 1 year before the screening visit or are surgically sterile. Females of childbearing potential* must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS®) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. Female patients must agree to practice two effective methods of birth control from the time of signing the informed consent form though 90 days after the last dose of study drug

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

- *Has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or*
- *Has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)*

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

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

3.1.9 Men must agree to use a latex condom during sexual contact with a female of childbearing potential even if they have had a successful vasectomy during the entire study treatment period and through *90 days* after the last dose of study drug **OR** agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

3.2 Exclusion Criteria

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

- Increased calcium levels (corrected serum calcium > 0.25 mmol/dL above the upper limit of normal or > 0.275 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)
- 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
- MRI with two or more focal lesion that is at least 5 mm or greater in size

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

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

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

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

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

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

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

3.2.8 Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of hepatitis B virus vaccine are eligible.

3.2.9 Major surgery within 14 days before first dose of ixazomib.

3.2.10 Known Amyloid involvement.

3.2.11 Myeloma-related central nervous system involvement.

3.2.12 Systemic treatment, within 14 days before the first dose of ixazomib with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

3.2.13 Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.

3.2.14 Grade 2 peripheral neuropathy or higher or grade 1 with pain on clinical examination during the screening period.

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

3.2.16 Previous treatment with ixazomib, or participation in a study with ixazomib whether treated with ixazomib or not.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC 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 subject must be taken off-study in

the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC 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 Project Manager. All sites should call the Project Manager to verify study status and slot availability.

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 Project Manager should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

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

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

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

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

NOTE: Same day treatment registrations will only be accepted with prior notice and discussion with DFCI.

5. TREATMENT PLAN

5.1 Treatment Regimen

Treatment will consist of 9 cycles of induction therapy followed by maintenance therapy for a total of 24 months. A treatment cycle is defined as 28 consecutive days.

For treatments cycle 1 and 2, a +/- 3 day window is allowed. For treatments cycle 3 through 24 a +/-7 day window is allowed.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Induction Cycles

Table 7: Ixazomib and Lenalidomide and Dexamethasone Combination (Cycles 1-9)

Agent	Pre-medications/ Precautions	Dose	Route	Schedule	Cycle Length
Ixazomib	Should not be taken with food	4 mg	Oral	Days 1, 8, 15	28 days
Lenalidomide	None	25 mg	Oral	Days 1–21 of each cycle	
Dexamethasone	Take with food; Recommended to be taken in the morning	40 mg	Oral	Days 1, 8, 15, 22	

Maintenance Cycles

Table 8: Ixazomib and Lenalidomide Combination (Cycles 10-24)†

Agent	Pre-medications/ Precautions	Dose	Route	Schedule	Cycle Length
Ixazomib	Should not be taken with food	4 mg*	Oral	Days 1,8, 15	28 days
Lenalidomide	None	15 mg**	Oral	Days 1–21 of each cycle	

* If patient was dose reduced during the induction phase for ixazomib below 4mg, then maintenance phase starts at that dose reduction and not at the higher 4 mg dose.

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

†After discussion with the overall principal investigator, high-dose dexamethasone may be re-added during maintenance due to biochemical progression (progressive increase in SPEP [25% and an absolute increase of 0.5g/dL] or UPEP [25% and an absolute increase of 200mg/24hours] on 2 successive evaluations as determined by the IMWG response criteria or documented progression by the FreeLite™ progressive disease criteria in the absence of serum or urine

involvement). If approved by the overall PI, dexamethasone should be given as an oral dose of 40mg on days 1, 8, 15, and 22.

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

Stem cell collection using standard mobilization procedures of the Institute can be performed for patients who are eligible and will be performed at the time of best remission or after 9 cycles of therapy. Patients may delay treatment for up to 3 weeks after stem cell collection is complete.

During maintenance, patients may return to clinic every 3 cycles beginning with cycle 10. If this option is utilized, a 3-month supply of ixazomib will be supplied by the investigational pharmacy at each visit. Lenalidomide may be shipped from the investigational pharmacy to the patient's home for each cycle the patient does not return to clinic, according to local practice.

5.2 Agent Administration

The order in which the drugs are administered does not matter.

5.2.1 **Ixazomib**

The ixazomib drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg and 2.0-, 0.5-, and 0.2 mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described in table 9 below:

Table 9: Ixazomib Capsule Description

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink
2.0 mg	Size 2	Swedish orange
0.5 mg	Size 3	Dark green
0.2 mg	Size 4	White opaque

For additional details, please see the ixazomib IB.

For more detailed information regarding ixazomib product information please refer to Section 8.1.

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 6.1).

Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of 2.3, 3.0 and 4.0 mg ixazomib. The prescribed administration of ixazomib doses in this study is 4 mg ixazomib in a 28-day cycle.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

5.2.1.1 Dose Delay or Interruption

Please refer to section 6.1 of the protocol

5.2.2 **Lenalidomide**

Lenalidomide will be given as a single daily oral dose of 25 mg per day on days 1–21 followed by a 7-day rest period for cycles 1–9 and 15 mg per day on days 1-21 for cycles 10–24. A window of +/-7 days is allowed, except cycles 1 and 2 which will be +/- 3 days. Dose modification guidelines are described in Section 6.2 (Dose Modifications/Delays).

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

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

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

5.2.2.1 Dose Delay or Interruption

Please refer to sections 6.1 and 6.2 of the protocol.

5.2.3 **Dexamethasone**

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

Dexamethasone will be given as a single oral dose on days 1, 8, 15, and 22 of each 28 day cycle during the induction phase of this study (Cycles 1-9 only).

Dexamethasone should be taken at approximately the same time each day. It is recommended that dexamethasone be taken in the morning to reduce insomnia. Each dose should be taken with food. If a dose of dexamethasone is vomited, the participant should continue with the regular schedule of the drug at the next dose. If a dose is missed and less than 12 hours has elapsed since the missed dose, the patient may take the dose for that day. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. A drug diary will be provided to participants to record oral administration of doses.

At the treating investigator's discretion, dexamethasone may be given as a split dose over 2 consecutive days.

5.2.3.1 Dose Delay or Interruption

Please refer to section 6.3 of the protocol.

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

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Medications and supportive care

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

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

- Stem cell mobilization will be allowed at the time of best response or at the end of induction therapy (after 9 cycles) for patients who are eligible for stem cell transplant. Standard mobilization treatment (with GCSF or with cyclophosphamide or plerixafor, etc) will be used based on Institutional guidelines. Patients may delay treatment for up to 6 to 8 weeks for mobilization purposes. Filgrastim is allowed per standard protocol for stem cell mobilization if stem cell mobilization will be performed. This will be allowed per standard procedure of stem cell collection per

Institutional guidelines.

- Use of white cell growth factors [Filgrastim or acceptable equivalent] is allowed for management of treatment induced neutropenia at physician discretion. Filgrastim should be given according to the ASCO guidelines. Pegfilgrastim is not to be used in replace of filgrastim.

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

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

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

- If nausea persists in spite of the use of standard antiemetics additional symptom management should be as per standard antiemetic guidelines.

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

- **Thromboprophylaxis is required for all participants**. Participants may receive daily aspirin administration (81 or 325 mg), daily enoxaparin (40 mgs), or low molecular weight heparin (type Innohep® 4500 UI anti-Xa as needed) or equivalent to decrease the risk of thromboembolic complications. Aspirin prophylaxis will be the preferred first choice unless contraindicated. It is recommended that if the platelet count falls below 30,000/mm3, thromboprophylaxis be held to minimize the risk of bleeding and then resumed when platelet counts are equal to or above this level.

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

- **Prophylaxis Against Risk of Reactivation of Herpes Infection virus:** Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other

antivirals may be initiated as clinically indicated at the discretion of the treating investigator. Other antivirals are also acceptable.

- **Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use** (Rationale: If there were to be a DDI with an inducer, ixazomib exposure would be less; therefore, there would be a reduced chance of an AE. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off ixazomib):
    - Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
    - Excluded foods and dietary supplements include St. John's Wort and Ginkgo Biloba
- The following procedures are prohibited during the study.
    - Any antineoplastic treatment with activity against MM, other than study drugs
    - Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)

5.4 Management of Clinical Events

- **Erythematous Rash With or Without Pruritus** Rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.
    - Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone $\leq$ 10 mg per day or equivalent) is permitted.
    - Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted
    - In line with clinical practice, a dermatology consult that include a biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously

developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines).

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

- **Thrombocytopenia.** Blood counts will be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Section 6.1). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

- **Neutropenia.** Blood counts will be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Section 6.1). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

- **Fluid Deficit.** Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

  - Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

- **Hypotension.** Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

- **Posterior Reversible Encephalopathy Syndrome.** One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

- **Transverse Myelitis.** Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded.

- **Pregnancy.** It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.
    - Female patients must meet 1 of the following:
        - Postmenopausal for at least 1 year before the screening visit, or
        - Surgically sterile, or
        - If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, or
        - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)
    - Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:
        - Practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or
        - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

5.5 Criteria for Taking a Participant Off Protocol Therapy

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

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

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

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

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

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

5.6 Duration of Follow Up

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

5.7 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Recommended Ixazomib Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

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

- ANC must be ≥ 1,000/μL.
- Platelet count must be ≥ 75,000/μL.
- All other clinically significant, study drug related non hematologic toxicity must have resolved to ≤ Grade 1 or to baseline condition

If the participant fails to meet the above-cited criteria for initiation of a new cycle of treatment during induction, dosing will be delayed for 1 week. At the end of that time, the participant should be re-evaluated to determine whether the above criteria have been met. If the participant continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate. The maximum delay for toxicity before treatment is permanently discontinued will be 3 weeks, however delays due to other circumstances should be discussed with the Principal Investigator. Delays of > 3 weeks must be discussed with the Principal Investigator. Re-treatment will be at the discretion of the Principal Investigator.

During maintenance, the above pre-treatment criteria must only be met every 3 months during cycles when a provider is seen. During cycles when the patient does not return to clinic, sites must follow local guidelines for pre-treatment criteria.

There is no specific pre-treatment criteria for lenalidomide during induction or maintenance. Sites should follow local guidelines for beginning a new cycle of treatment with lenalidomide.

If any one of the study medications is permanently discontinued for toxicity, the patient may remain on the study at the discretion of the investigator.

Table 10: Ixazomib Dose Adjustments

Dose Level	Dose
Starting Dose	4.0 mg
-1	3.0 mg
-2	2.3 mg
-3	Discontinue

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

A delay of up to 14 days will be allowed for participants for non-AE related events (i.e.; vacation, family emergency, etc) after discussion with the overall PI.

For both Ixazomib and lenalidomide the investigator may discuss considerations for dose modifications and symptom management with the Principal Investigator.

Treatment modifications due to Ixazomib or lenalidomide-related AEs are outlined in Tables 11 and 12.

Table 11: Ixazomib and Lenalidomide Dose Adjustments for Hematologic Toxicities

Within-Cycle Dose Modifications (other than Day 1)	
Criteria	**Action**
Platelet count ≤ 30,000/μL **or** **ANC ≤ 500/μL**	• Ixazomib dose should be held. Lenalidomide dose should be held. • Complete blood count (CBC) with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the pre-specified values on at least 2 occasions. • Upon recovery (1st occurrence), lenalidomide may be reinitiated with 1 dose level reduction depending on the attribution of the toxicity to the study agent. Do not dose reduce ixazomib. Upon recurrence of the toxicity (2nd occurrence), ixazomib may be reinitiated with 1 dose level reduction depending on the attribution of the toxicity to the study agent.
Dose Modifications for Subsequent Treatment Cycles on Day 1	
Criteria	**Action**
Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.3.1 **ANC < 1,000/μL** **Platelet count < 75,000/μL**	• Hold ixazomib and lenalidomide until resolution as per criteria Section 6.1. • Upon recovery, reduce lenalidomide 1 dose level, depending on the attribution of the toxicity to the study agent. If lenalidomide has been reduced during the cycle, consider a dose reduction of ixazomib upon reinitiating the subsequent cycle. • The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the PI.
Dose Modifications for Subsequent Treatment Cycles	
Criteria	**Action**
All Hematologic Toxicities	For any hematologic toxicity that occurs during a cycle but recovers in time for the start of the next cycle: • If dose was reduced within the cycle, start the next cycle at that same dose. • If due to toxicity timing, ie, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of that cycle. • **Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.**

Table 12: Ixazomib and Lenalidomide Dose Adjustments for Non-Hematologic Toxicities

Adverse Event	Severity	Action on Study Drug	Further Considerations
New or Worsening Peripheral Neuropathy **(CTCAE v.4.0)**	Grade 1 Peripheral Neuropathy	No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only deep tendon reflexes or parasthesia
	Grade 1 Peripheral Neuropathy with pain or Grade 2	Hold Ixazomib until resolution to Grade ≤ 1 without pain or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL)
	Grade 2 Peripheral Neuropathy with pain or Grade 3	Hold Ixazomib until resolution to Grade ≤ 1 without pain or baseline Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated
	Grade 4 Peripheral Neuropathy	Discontinue Ixazomib	Grade 4 signs and symptoms: Life threatening consequences; urgent intervention indicated
Rash	Grade 2	Symptomatic recommendations as per section 5.3 and 5.4	
Non-Hematologic toxicities judged to be related to study drug	Grade 3	Hold Ixazomib or lenalidomide depending on the attribution until resolution to Grade < 1 or baseline	Symptomatic recommendations noted in Section 5.3 and 5.4
		If not recovered to < Grade 1 or baseline within 3 weeks: Reduce Ixazomib or lenalidomide depending on the attribution to next lower dose upon return to < Grade 1 or baseline	

Table 12: Ixazomib and Lenalidomide Dose Adjustments for Non-Hematologic Toxicities

Adverse Event	Severity	Action on Study Drug	Further Considerations
Non-Hematologic toxicities judged to be related to study drug	Grade 3	Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 3 weeks • Hold study drug until resolution to Grade < 1 or baseline • Reduce study drug to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Non-Hematologic toxicities judged to be related to study drug	Grade 4	Consider permanently discontinuing the offending study drug (depending on attribution).	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

If the patient discontinues either Ixazomib or lenalidomide, he or she does not need to come off protocol therapy.

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

6.2 Lenalidomide

See dose modifications described above in tables 11 and 12.

Table 13: Lenalidomide Dose Reduction

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

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

6.3 Dexamethasone

Table 14: Dexamethasone Dose Modifications

Gastrointestinal		
Dyspepsia	Grade 1-2	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone by 1 dose level
Gastric or Duodenal Ulcer **Gastritis**	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequate controlled. Restart and decrease 1 dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Acute Pancreatitis	All Grades	Discontinue dexamethasone and do not resume.
Cardiovascular		
Edema (limiting function and unresponsive to therapy or anasarca)	≥ Grade 3	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; If edema persists despite above measures, decrease dose another level and do not resume if symptoms persist despite second reduction.
Neurology		
Confusion or Mood Alterations (interfering with function +/- interfering with activities of daily living)	≥ Grade 2	Hold dexamethasone until symptoms resolve. Restart with 1 dose level reductions. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal		
Muscle Weakness (symptomatic and interfering with function +/- interfering with activities of daily living)	≥ Grade 2	Decrease dexamethasone 1 dose lever. If weakness persists despite above measures decrease by 1 dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic		
Hyperglycemia	≥ Grade 3	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose level by 1 dose level until levels are satisfactory.

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

Table 15: Dexamethasone dose reduction

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

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

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Definitions

Adverse Event Definition

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

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

Serious Adverse Event Definition

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

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

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

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

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

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

7.2 Expected Toxicities

7.2.1 Adverse Events List(s)

7.2.1.1 Adverse Event List of Ixazomib

As of 27 March 2013, preliminary clinical data is available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported

treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

7.2.1.2 Adverse Event List for Lenalidomide

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

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

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

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

7.2.1.3 Adverse events list of Dexamethasone

Events that have occurred in 10-15% of individuals treated with dexamethasone include increased appetite, weight gain, sleep disturbance, hypertension, fluid retention, ankle swelling, bruising, infection, mood changes, slow wound healing, depression, and hyperglycemia, which may lead to fatigue, weight loss, excessive thirst and frequent urination. Events that have occurred in 1-9% of individuals treated with dexamethasone include loss of appetite, muscle twitching, increased thirst, frequent urination, increased perspiration, diarrhea, nausea, headache, bone thinning, spinal fracture or fracture of bones, tachycardia, fungal infections. Events that have occurred in <1% of individuals treated with dexamethasone include blurred vision, personality changes, stomach ulcers with bleeding that may cause hematemesis, blood in the stool and abdominal pain. Other, less frequent, events may include bowel perforation, irritation and bleeding of the esophagus, heart failure, allergic reaction that may lead to facial redness, shortness of breath, abdominal cramps and hypotension, convulsions, brain swelling, dizziness, cataracts, glaucoma and increased blood pressure in the eye, development of diabetes, pancreatic inflammation, abdominal swelling, hypokalemia, DVT or PE, malaise, swelling and/or redness of skin, allergic skin reactions, itching, hirsutism, muscle weakness or loss of muscle mass, rupture of tendons, menstrual cycle disturbances, facial puffiness, leading to the appearance of a “moon face” hormonal disturbances, and hiccups.

7.3 Adverse Event Characteristics

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

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

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4 Expedited Adverse Event Reporting

7.4.1 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.

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

7.5 DF/HCC Expedited Reporting Guidelines

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

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

Attribution	**Table 17- DF/HCC Reportable AEs**				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 hours of learning of the event.					

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

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

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. The investigator must immediately notify the Millennium and Celgene (or designee) Medical Monitor of this event and complete and forward an SAE Form to Millennium and Celgene (or designee) within 24 hours and in accordance with SAE reporting procedures described in this section.

7.6 Procedures for Reporting Serious Adverse Events to Millennium

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dose of ixazomib. Any SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, the principal investigator [redacted] also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported in English to Millennium Pharmacovigilance (or designee):

Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The sponsor-investigator must fax or email the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.
Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s), as soon as possible but no later than 4 calendar days of such communication.

SAE and Pregnancy Reporting Contact Information

[redacted]

Suggested Reporting Form:

- SAE Report Form (provided by Millennium)
- US FDA MedWatch 3500A:
  - http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

Pregnancy

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

7.7 Product Complaints

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

For Product Complaints

[redacted]

Hours: Mon-Fri 9AM – 7PM EST (US)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance

7.8 Expedited Reporting to Celgene

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious Adverse Event Definition

Serious AE (SAE) means any Adverse Event which:

- Results in death (including also spontaneous and therapeutic abortion, fetal and neonatal death, any death of an infant which occurs within 28 days of birth subsequent to *in utero* exposure to Study Drug),
- Is life-threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly or birth defect.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-MM-PI-006919) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Pregnancy
Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (provided by Millennium)

Male Subjects

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

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
[redacted]

Overdose

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

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

PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose
SC	10% over the protocol-specified dose

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

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

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

7.8.1 Protocol-Specific Expedited Adverse Event Reporting Exclusions

There are no protocol specific exclusions.

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

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

7.10 Expedited Reporting to Hospital Risk Management

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

7.11 Routine Adverse Event Reporting

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

8. PHARMACEUTICAL INFORMATION

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

8.1 Ixazomib

8.1.1 Description

The chemical name is: B-[(IR)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]boronic acid. Ixazomib, also known as MLN9708 and Ninlaro, is an oral proteasome inhibitor. The molecular formula is C20H23BCl2N2O9. The molecular weight is 517.12.

8.1.2 Form

Ixazomib is provided by Millennium in capsule form as outlined in the table below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink

The capsules are individually packaged using cold-form foil-foil blisters that are in a child-resistant carton. There are 3 capsules in each wallet/carton.

8.1.3 Storage and Stability

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site as directed on the label. Do not store about 30°C. Do not freeze. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, ixazomib capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time, unless in maintenance, when they may receive 3 cycles worth. Patients should be instructed to store the medication as directed on the label for the duration of each cycle. Do not store above 30°C. Do not freeze. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

8.1.4 Handling

Because ixazomib is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules.

8.1.5 Availability

The study drug ixazomib capsules will be provided by Millennium free of charge. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

8.1.6 Preparation, Reconstitution, and Dispensing

Ixazomib is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling ixazomib capsules.

During Induction, 1 cycles worth of ixazomib will be provided at each cycle day 1, and patients will not be required to take doses in clinic.

During maintenance, patients may return to clinic every 3 cycles beginning with cycle 10. If this option is utilized, a 3 month supply of ixazomib will be supplied by the investigational pharmacy at each visit.

Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules.

8.1.7 Administration

Ixazomib will be given daily on days 1, 8, and 15 of each 28 day cycle on an out-patient basis.

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

Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

8.1.8 Ordering

The investigator or designee will order ixazomib from Millennium, according to the ordering instructions provided by company.

8.1.9 Accountability

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

8.1.10 Destruction and Return

Investigational ixazomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

8.2 Lenalidomide

8.2.1 Description

Lenalidomide (REVLIMID®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H- isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure: 3-(4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3.

8.2.2 Form

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

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

8.2.3 Storage and Stability

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

8.2.4 Handling

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

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

8.2.5 Availability

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

site by the drug courier Biologics and be distributed to the patient through the research side of the pharmacy of that site.

Further information about the Revlimid REMS® program is available at www.celgeneriskmanagement.com.

8.2.6 Preparation

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

8.2.7 Administration

Lenalidomide will be given daily on days 1-21 of each 28 day cycle
At all times when dispensing lenalidomide protocol therapy, study site personnel will review the instructions, printed on the packaging, with participants.

8.2.8 Ordering

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

Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Lenalidomide will be shipped directly to the clinic site. Bottles will contain a sufficient number of capsules for one cycle of dosing**.**

During maintenance, patients may return to clinic every 3 cycles beginning with cycle 10. If this option is utilized, lenalidomide may be shipped from the investigational pharmacy to the patient's home for each cycle the patient does not return to clinic, according to local practice.

8.2.9 Accountability

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

8.2.10 Destruction and Return

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

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

8.3 Dexamethasone

8.3.1 Description

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.

The molecular weight for dexamethasone is 392.47. It is designated chemically as 9- fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. Dexamethasone is stable in air and almost insoluble in water.

8.3.2 Form

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

8.3.3 Storage and Stability

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

8.3.4 Handling

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

8.3.5 Availability

Dexamethasone supply will be obtained through commercial supply.

8.3.6 Preparation

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

8.3.7 Administration

During induction therapy, participants will receive dexamethasone as a single oral daily dose on Days 1, 8 and 15 and 22 of cycles 1-9.

8.3.8 Ordering

Dexamethasone will be ordered from retail pharmacy using commercial drug supply.

8.3.9 Accountability

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

8.3.10 Destruction and Return

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

This trial will provide samples SMM patients treated with Ixazomib, lenalidomide and dexamethasone to comprehensively characterize the MM genome and immune cells function and define molecular events driving development and progression of MM. Please see Appendix D for a listing of further proposed correlative studies.

We will attempt to obtain samples on all patients who consent to the optional studies at the following time points: before therapy, at the end of cycle 9 or at the time of response confirmation if prior to Cycle 9, 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. Participants may decline sample collection at any timepoint.

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.

Peripheral blood and bone marrow samples will be collected per the collection time described in the table of sample collection. Minimum residual disease (MRD) will be assessed as standard of care at the time of CR or VGPR by Adaptive using spiked-in reference sequences. Clinical bone marrow aspirate samples should be collected per institutional guidelines and sent to Adaptive for analysis.

Single-cell sequencing will be performed on patients prior to treatment and at the end of induction.

Participants either identified as responders, or non-responders will have an additional timepoint sequenced, to be determined, after review of response to therapy. All single-cell Droplet RNA sequencing (Drop-seq) will be performed by the Broad Institute. We will first use drop-seq of CD138+ cells and CD138-ve CD45+ or CD138-ve CD45-ve cells from viably frozen cells in DMSO.

9.1 Bone Marrow Aspirate Samples

Collection of bone marrow aspirate specimens for exploratory analysis 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.

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

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

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

9.1.1 Shipping Instructions:

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

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

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 [redacted] to notify of an incoming shipment.

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

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

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

9.2 Peripheral Blood Samples

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

9.2.1 Specimens Required: 2 x 10 mL Purple Top Tubes (K2EDTA) and 1 x 6 mL red top tube, should be collected Mondays to Thursdays for same-day shipment.

9.2.2 Shipping Information: Label all specimens with the following:

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

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

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

Processing Information:

Invert each tube 5 times at blood collection to ensure adequate mixing of anticoagulant with blood immediately after the blood collection. Package tubes at room temperature and wrap in a liberal amount of paper towel around the tubes to ensure adequate insulation of the specimen(s) and absorption in the event of a breakage. Place wrapped specimen in a biohazard labeled Ziploc bag with a fridge pack and zip close. Wrap bubble wrap around the bag and place in a cardboard box. If space remains in the box, stuff with extra paper towel to reduce shifting of samples. Complete the shipping requisition form using the address listed below. Prepare the package for shipping, applying packing tape as needed. Ship the package using FedEx or UPS next day or overnight delivery the same day the sample was collected. Please only ship Monday-Thursday, as the lab is only able to accept Saturday shipments with 1 week advance notice. With each shipment, please include the following:

1. An inventory sheet including a complete list of samples shipped (patient number, timepoint, study #) must accompany each shipment. Please sign and date the form, and retain a copy for site record maintenance. **See Appendix C for Sample Requisition Form**
2. An electronic copy (Word or Excel) of the sample list must also be sent via email and include the tracking number of the package. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.

3. Please email Rachel Styles (rachell_styles@dfci.harvard.edu) 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:**

[redacted]

Please retain a copy for site record maintenance.

10. STUDY CALENDAR

Screening evaluations are to be conducted within 28 days prior to registration. If bone marrow biopsy, research aspirate, and imaging assessments are completed within 6 weeks of registration, they do not need to be repeated at screening. Baseline assessments are to be conducted on C1D1 of initial therapy. C1D1 must occur within 6 weeks of registration. 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. Study assessments and medications should be administered within +/- 3 days (during cycles 1-2) and +/- 7 days (during cycles 3-24) of the protocol-specified date, unless otherwise noted. See below for detailed scheduled of assessments. Study medications will be administered according to the schedule and guidelines outlined in Section 5.

	Pre-registration		**Cycles 1-24 (28 days)** [3]				**Event Monitoring**
Tests and procedures	**≤ 28 days prior to registration**	**≤ 21 days prior to registration**	**Day 1 of cycles 1-9**[1]	**Every 3 months for Cycles 10-24**	**Cycle 10 Day 1/ Or to confirm CR**[8]	**End of Tx (± 2 weeks)**	**Every 3 Months (± 2 weeks)**[13]
History and exam, height, weight. Performance Status	X		X	X		X	X
Toxicity Notation			X	X		X	
Hematology group (WBC w/ diff, PLT, Hgb, ANC)		X	X	X		X	X
Chemistry[4]		X	X	X		X	X
Direct & total bilirubin[2]		X	X	X		X	
Free light chain assay		X	X	X		X	X
Serum and Urine Immunofixation (SPEP and UPEP) with quantitative immunoglobulins[9]		X	X	X		X	X
β2M and LDH		X	X	X		X	
Metastatic Bone Survey and MRI of the Full Spine ***OR*** PET/CT [12]	X					X	
EKG		X				X	
Serum or urine pregnancy test[11]		X	X				
Unilateral bone marrow aspirate and biopsy[5]	X				X	X	
Research bone marrow aspirate[6]	X[5]				X[6]	X[6]	
Research Blood[7]	X[7]		X[7]	X[7]	X[7]	X[7]	
Buccal Swab[10]	X						

1- Cycle 1, Day 1 laboratory values need to meet eligibility criteria
2- Direct bilirubin to be obtained if total bilirubin is abnormal
3- Scheduling allows for +/- 3 days cycles 1-2 and +/- 7 days for cycle 3 and beyond
4- Chemistry includes sodium, potassium, chloride, bicarbonate, bun, creatinine, calcium, glucose, albumin, ALT (SGPT), total protein, AST (SGOT), total bilirubin, magnesium, and phosphorus
5- These procedures should also be done at any time during the course of the study to confirm CR Aspirate should be collected and sent out to Adaptive for MRD analysis at baseline and at time of VGPR or suspected CR
6- Research bone marrow aspirate and biopsy at the same time of clinically indicated bone marrow biopsy and to confirm response
7- Peripheral blood samples for correlative studies
8- If BM biopsy performed within 3 weeks of C10D1, or confirmation of CR BM biopsy performed within 3 weeks of stem cell collection, do not need to repeat BM biopsy
9- If the participant's disease response is not followed primarily via a UPEP and Urine immunofixation, these tests may be done only at screening, end of treatment, and as clinically indicated during treatment and follow-up
10-The buccal swab can be performed at any timepoint during study participation
11-Pregnancy tests are only required for women of childbearing potential 10-14 days prior to registration, 24 hours prior to prescribing lenalidomide for C1 and every day 1 post C1

12-A CD of scans at screening and end of treatment is required to be sent to the lead site for central review Screening scans should be sent with the eligibility packet to the lead site- This requirement includes a full body skeletal survey in addition to spinal MRI OR the patient may have only a low dose PET CT
Note: Research blood and bone marrow studies of all cycles after cycle 1 are voluntary and do not exclude patients from participating
13 – Participants unable to come in for follow up every 3 months can be allowed to come in every 6 months for follow up at PI discretion in accordance with standard of care follow-up frequency

11. MEASUREMENT OF EFFECT

11.1 Development of symptomatic disease

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

- Increased calcium levels (corrected serum calcium >0.25 mmol/dL above the upper limit of normal or >.275 mmol/dL) due to myeloma
- Renal insufficiency (attributable to myeloma);
- Anemia (Hb 2g/dL below the lower limit of normal or <10g/dL) due to myeloma
- Bone lesions (lytic lesions or generalized osteoporosis with compression fractures)
- Or any MYELOMA DEFINING EVENTS (MDE) as follows:
    - Clonal bone marrow plasma cell percentage > 60%[8]
    - An abnormal FLC-ratio ≥100 (involved kappa) or <0.01 (involved lambda)[9]
    - 2 or more focal lesions on MRI or PET-CT studies[10,11]

For measurement of response:
In this study, patients **must** have measurable disease (see Section 11.2.1). The disease response will be assessed using criteria based on the International Myeloma Working Group Uniform Response Criteria in Section 11.2.3.1. If the only measurable parameter is serum immunoglobulins free light chain (FLC), the participant will be followed by FreeLite™ Disease Response Criteria provided in Section 11.2.4.

Disease response by the Modified EBMT Response Criteria in Section 11.2.5.2 will also be collected on participants as a secondary measure.

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

11.2 Antitumor Effect

11.2.1 Disease Parameters

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

- Serum M-protein ≥ 0.5 g/dl
- Urine M-protein ≥ 200 mg/24 h
- Serum FLC assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) provided serum FLC ratio is

abnormal.

11.2.2 Methods for Evaluation of Measurable Disease

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

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

11.2.3 Response Criteria

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

11.2.3.1 International Myeloma Working Group Response Criteria

Response criteria for all categories and subcategories of response except CR are applicable only to patients who have 'measurable' disease, as defined in Section 11.1.1 All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

Response	Criteria for Response
Stringent CR (sCR)	CR as defined below plus normal free light chain ratio and absence of clonal cells in bone marrow* by immunohistochemistry or immunofluorescence.** *Confirmation with repeat bone marrow biopsy is not needed. **Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/l ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of > 4:1 or < 1:2.
Complete Response (CR)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow. *Confirmation with repeat bone marrow biopsy is not needed.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 hours.

Partial Response (PR)	≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by > 90% or to < 200mg per 24 hours. If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (definition of measurable disease in Section 10.2.3). If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%. In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required.
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease. This is not recommended as an indicator of response; stability of disease is best described by providing the time to progression estimates.
Progressive Disease (PD)	> 25% increase of serum M-protein (which must also be an absolute increase of ≥ 0.5 g/dL) and/or urine M-protein (which must also be an absolute increase of ≥ 200 mg/24hr). If serum and urine M-protein are unmeasurable, there must be an absolute increase of ≥ 10 mg/dL between involved and uninvolved FLC levels. PD is also measured by an absolute increase in bone marrow plasma cells ≥ 10%. In addition to the above listed criteria, progression may also be measured by a definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas or development of hypercalcemia (corrected serum calcium ≥ 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.

*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.

11.2.4 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.

11.2.4.1 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[68].

11.2.4.2 Modified EBMT Response Criteria

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

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

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

a Based on the criteria reported by Blade et al., 1998.

b Per Blade *et al*., 1998, if absence of the monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow except in participants with nonsecretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.

c Per Blade *et al*., 1998, skeletal X-Rays are not required for the definition of response, but if performed there must be no evidence of progression of bone disease (no increase in size or number of lytic bone lesions).

d It is suggested that the reference point for calculating any increase should be the lowest value of the preceding confirmed response (MR, PR or CR) or the baseline value if there is no previous confirmed response.

e Other clinical data may be requested by the IRC, as necessary, to assess the cause of the hypercalcemia.

11.2.5 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.

11.2.6 Progression-Free Survival

Progression-Free Survival (PFS): the primary endpoint in this study. PFS is defined as the time from randomization to the disease progression or death from any cause. Patients who have not progressed or died are censored at the date last known progression-free.

11.2.7 Response Review

Central review of disease response assessments is not planned.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

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

12.2 Data Safety Monitoring

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

with the Overall PI and study team.

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

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoint of this phase II study is to determine the proportion of patients with high-risk smoldering multiple myeloma (SMM) patients who are progressive free at 2 years after receiving therapy with Ixazomib/lenalidomide and dexamethasone. The secondary objectives include toxicities, objective response rate, time to progression, duration of response, and overall survival.

The proportion of patients who achieve progression free at 2 years will be compared to the rate published for the high-risk SMM. By the Mayo Clinic model for risk factors, the median time to progression for patients with high-risk SMM was only 1.9 years. Therefore, a 2-year progression-free rate of 50% will not be considered promising. We assume that the true 2-year progression-free rate is 70%. With a type I error of 5% and power of 90%, 53 eligible patients will be required in a single-stage design. The probability of concluding that the treatment is effective if the true rate is 50% is 0.05 and is 0.91 if the true rate is 70%. Assuming an ineligibility rate of 5%, we will accrue 56 patients to the trial in order to have 53 eligible patients. Any patients who are registered, but do not start study treatment will be replaced.

13.1.1 Analysis of Primary Endpoint

Time to progression (TTP) is defined as the time from protocol therapy initiation until documented progression, censored at date last known progression-free for those who have not progressed. At time of final analysis, the 2-year progression-free rate will be estimated using the Kaplan-Meier method with 95% confidence interval. All patients who have received one dose of study treatment will be included for the TTP analysis, including those who die or are lost to follow-up within 2 years.

13.1.2 Analysis of Secondary Endpoints

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

To estimate the duration of response (time from objective response to disease progression or death, or date last known progression-free and alive for those who have not progressed or died), progression-free survival (time from protocol therapy initiation to the disease progression or death from any cause, censored at date last known progression free for those who have not progressed or died), and overall survival (time from protocol therapy

initiation to death or date last known alive), the Kaplan-Meier method will be used.

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

13.2 Sample Size, Accrual Rate and Study Duration

A total of 56 patients will be enrolled. Any patients who are registered but do not start study treatment will be replaced. We expect 1.5 years of active accrual (approximately 2 patients per month) and 3 years of follow-up of patients.

The final analyses of progression-based endpoints, such as estimating the 2-year progression-free rate and estimating the TTP distribution, will be conducted at the end of the study, which will occur after either all subjects have progressed or died or 3-years after the initiation of therapy of the last subject enrolled, whichever occurs first.

13.3 Stratification Factors

There are no stratification factors.

13.4 Interim Monitoring Plan

The study will be monitored by the DFCI Data Safety Monitoring Committee (DSMC). The DSMC will meet at least four times a year and more often if needed (e.g., for safety review). For each meeting, the study will be reviewed for safety and progress toward completion. Copies of the toxicity reports prepared by the DSMC meetings will be distributed to the Principal Investigator. The Principal Investigator will then distribute to subinvestigators. Any DSMC recommendations for changes to the study will be distributed to the Principal Investigator and then circulated to sub- investigators by the Principal Investigator. No interim analysis of the outcome data is planned.

13.5 Stopping Rule for Safety

All participants will be evaluable for treatment-related toxicity from the time of therapy initiation. The serious adverse event (SAE) 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.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: SPECIMEN COLLECTION SCHEDULE

Sample Time Point[2]	Container[1,]	Sample Type	Shipping Method	Recipient
Baseline	3 x 10mL Purple Top 1 x 6mL Red Top	Peripheral Blood	Fridge pack same day	DFCI Bone Marrow Sample
	2x10mL Purple Top 1x3mL Purple Top	Bone Marrow Aspirate		
	1x buccal swab	Saliva	Ambient same day	
Cycle1 Day 1 (Pre Dose)	2 x 10mL Purple Top 1 x 6mL Red Top	Peripheral Blood	Fridge pack same day	DFCI
Cycle 2-9 Day 1, Cycle 10+ every 3 cycles (i.e. Cycle 13, 16, 19, etc.)	2 x 10mL Purple Top 1 x 6mL Red Top	Peripheral Blood	Fridge pack same day	DFCI
End of Cycle 9 (Cycle 10 Day 1)	2 x 10mL Purple Top 1 x 6mL Red Top	Peripheral Blood	Fridge pack same day	DFCI
	2 x 10mL Purple Top	Bone Marrow Aspirate		
Confirm Complete Response [3]	3 x 10mL Purple Top 1 x 6mL Red Top	Peripheral Blood	Fridge pack same day	DFCI Bone Marrow Sample
	2 x 10mL Purple Top 1 x 3mL Purple Top	Bone Marrow Aspirate		
End of Treatment and/or Disease Progression	2 x 10mL Purple Top 1 x 6mL Red Top	Peripheral Blood	Fridge pack same day	DFCI
	2 x 10mL Purple Top	Bone Marrow Aspirate		
Clinically Indicated	2 x 10mL Purple Top	Bone Marrow Aspirate	Fridge pack same day	DFCI

[1] Purple Top= K2EDTA Tube; Red Top= No Additive
[2] Samples at all time points are voluntary, and do not exclude patients from treatment
[3] For definition of Complete Response, please refer to section 11.2.3.

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.

Ship specimen(s) to: [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/ Kit		
☐ Cycle 1-24 Day 1 Specify Cycle_____	☐ Blood	_____ Red Top _____ Purple Top		
☐ Confirm Response	☐ Blood ☐ Aspirate	_____ Red Top _____ Purple Top		
☐ Cycle 10 Day 1 (end of Cycle 9)	☐ 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: ADDITIONAL CORRELATIVE STUDIES PROPOSED

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. Briefly, somatic single nucleotide variants are determined using the MuTect algorithm. 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. 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, and open vs. closed chromatin status. Focal as well as arm-level copy number variations will be determined based on whole exome sequencing and subsequent application of the GISTIC algorithm.

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. 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.

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

4. **Integration of clinical correlation with genomic data obtained from these samples compared to those obtained from the PCROWD trial where MGUS and SMM samples are obtained and patients are followed for observation.** Here, we plan to use a portal along with infrastructure support from Celgene to correlate the data obtained from the RV-CL-MM-PI-006919 trial along with samples obtained from patients on observation only [redacted]

DFCI IRB Protocol #: 16-313

APPENDIX E*:* DANA-FARBER/HARVARD CANCER CENTER MULTI-CENTER DATA AND SAFETY MONITORING PLAN

TABLE OF CONTENTS

1. INTRODUCTION

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

1.1 Purpose

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

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

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

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

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

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

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc.) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

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

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

2. GENERAL ROLES AND RESPONSIBILITIES

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

2.1 DF/HCC Sponsor

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

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (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, 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.
- 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 Federal Wide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc.) and maintain documentation all relevant communications.

2.3 Participating Institution

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

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

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.

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

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

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

3.1 Protocol Distribution

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

3.2 Protocol Revisions and Closures

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

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

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

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

3.3 Informed Consent Requirements

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

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to

submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

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

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

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

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

3.6 Participant Confidentiality and Authorization Statement

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

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB and 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

Please see sections 4.3 and 4.4 of the protocol document for specific guidelines on the registration process and requirements.

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

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 7.

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

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

3.9.2 Guidelines for Processing IND Safety Reports

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

3.10 Data Management

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

3.10.1 Data Forms Review

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

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

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

4. REQUISITIONING INVESTIGATIONAL DRUG

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

Participating Institutions should order their own agent regardless of the supplier. (i.e., NCI or a pharmaceutical company.)

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

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

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the 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. At a minimum, the DF/HCC Lead Institute, or designee, will monitor each participating site twice a year while patients are receiving treatment. Should a Participating Institution be monitored once and then not accrue any additional patients or participant visits, then a second monitoring visit may not be necessary.

Additionally, regular and ongoing communication with Participating Institutions will be accomplished by holding all site teleconferences at least monthly. An agenda and the minutes from the meeting will be supplied to all call participants. The Lead Institution will keep in close touch with the Participating Institutions via email and phone.

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

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

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The expectation for this study is that each site should accrue three patients per site/annually.

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.