A Phase II Study of IRD (Ixazomib, Lenalidomide, & Dexamethasone) for Consolidation Therapy Post Autologous Stem Cell Transplantation followed by Maintenance Ixazomib or Lenalidomide for Multiple Myeloma

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Study Drug(s): Ixazomib
Lenalidomide
Dexamethasone

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Principal Investigator Signature Page

Principal Investigator:

Signature of Investigator	Date
Printed Name of Investigator	

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

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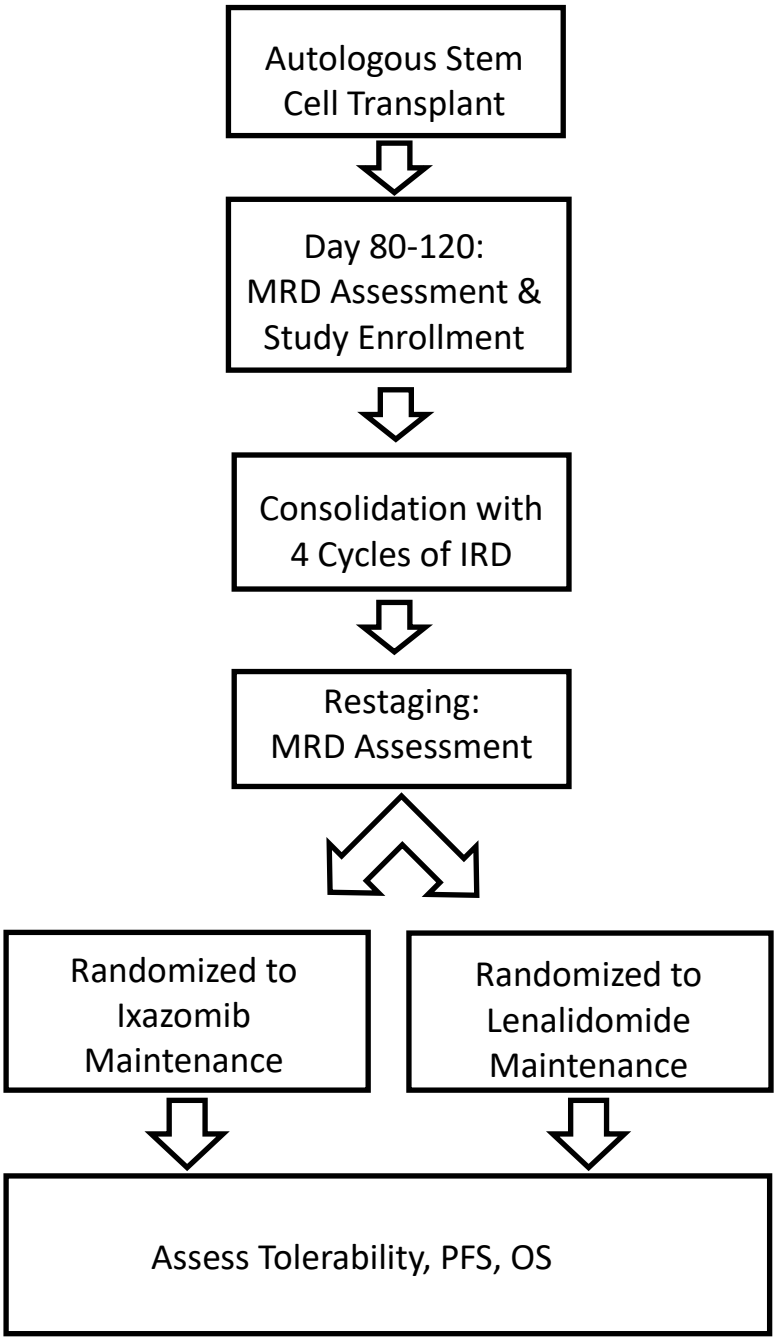
STUDY SCHEMA



PROTOCOL SUMMARY

Study Title: A Phase II Study of IRD (Ixazomib, Lenalidomide, & Dexamethasone) for Consolidation Therapy Post Autologous Stem Cell Transplantation followed by Maintenance Ixazomib or Lenalidomide for Multiple Myeloma

Phase: II

Number of Patients: ~240

Primary Objective

- To determine the improvement in MRD-negative rate after 4 cycles of IRD consolidation

Secondary/Exploratory Objectives

- To determine the MRD-negative rate after ASCT
- To evaluate the toxicity, response rate, PFS, and OS of IRD consolidation
- To collect pilot data to compare toxicity, response rate, PFS, OS, and the rate of MRD-positive to MRD-negative conversion between the two maintenance arms
- To evaluate the association of PFS and OS with MRD-negativity and MRD-positivity prior to consolidation and after 4 cycles of IRD consolidation
- To evaluate the relationship between HEVYLITE assay results with response and MRD status
- To evaluate the effect of ixazomib maintenance on the immune system

Overview of Study Design: Patients will undergo standard of care ASCT with conditioning regimen determined by the treating physician per institutional guidelines. The ASCT is not considered part of this study. Consolidation therapy will begin on between Day 80 and Day 120 following ASCT and will consist of four 28-day cycles of IRD (ixazomib, lenalidomide, & dexamethasone). Barring dose modifications for toxicity, 4 mg of ixazomib and 40 mg of dexamethasone will be administered on Days 1, 8, and 15, and 15 mg of lenalidomide will be administered on daily on Days 1-21.

Following completion of consolidation therapy, patients will undergo restaging and will be randomized on a 1:1 basis to maintenance therapy with ixazomib or lenalidomide. Patients will be stratified based on MRD status at restaging (MRD-positive v. MRD-negative).

Barring dose modifications for toxicity, ixazomib maintenance will consist of 4 mg administered on Days 1, 8 and 15 of each 28-day cycle, and lenalidomide maintenance will consist of 10 mg daily on Days 1-28 for the first three 28-day cycles and 15 mg daily for all further cycles. Maintenance therapy with either ixazomib or lenalidomide will continue until the patient experiences disease progression or unacceptable toxicity.

Study Population: Patients between the ages of 18 and 70 years of age (inclusive) at time of enrollment with a histologically confirmed diagnosis of symptomatic multiple myeloma, who have received at least two cycles of any regimen as initial systemic therapy for multiple myeloma and are within 2-16 months of the first dose of initial therapy who provide voluntary written consent.

Duration of Study: Three years to complete accrual; approximately 7 year patient participation; therefore 10 years total.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Definition
°C	degrees Celsius
ADR	adverse drug reaction
AE	adverse event
AL	primary amyloidosis
ALT	alanine aminotransferase/ serum glutamic pyruvic transaminase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the plasma concentration versus time curve
BCRP	Breast cancer resistant protein
BSA	body surface area
CL	clearance, IV dosing
cm	centimeter
CR	complete response
CRF	case report form
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
GI	Gastrointestinal
GCP	Good Clinical Practices
HRPO	Human Research Protection Office
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IRB	institutional review board
IRD	ixazomib, lenalidomide, and dexamethasone
ITT	intent-to-treat
IV	intravenous
m^2	square meters
MFC	multiparameter flow cytometry
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
mL	milliliter
MM	multiple myeloma

Abbreviation	Definition
mm^3	cubic millimeters
MRD	minimal residual disease
NDMM	newly diagnosed multiple myeloma
NYHA	New York Heart Association
OS	overall survival
PD	progressive disease
PFS	progression-free survival
Pgp	P-glycoprotein
PO	*per os*; by mouth (orally)
PR	partial response
QASMC	Quality Assurance and Safety Monitoring Committee
RP2D	recommended phase 2 dose
RRMM	Relapsed/Refractory Multiple Myeloma
SAE	serious adverse event
sCR	stringent complete response
SD	stable disease
SMA	safety management attachment
TEAE	treatment emergent adverse event
T_{max}	single-dose time to reach maximum (peak) concentration
UPN	unique patient number
VGPR	very good partial response
VTE	venous thromboembolism

1.0 BACKGROUND AND RATIONALE

1.1 Multiple Myeloma

Multiple myeloma (MM) is a multifocal plasma cell neoplasm resulting from the clonal expansion of terminally differentiated B-cells. The disease is characterized by a serum or urine monoclonal protein and skeletal destruction with osteolytic lesions, bone pain, pathologic fractures, and hypercalcemia. Recurrent infections from depressed normal immunoglobulin production, renal dysfunction from light chain production, and anemia from generalized marrow involvement are also common. In the United States, MM is the second most common hematologic malignancy behind non-Hodgkin's lymphomas with an estimated 15,270 new cases and 11,070 deaths in 2004 [1].

Progress in the treatment of MM has been modest since the introduction of melphalan more than 25 years ago. Melphalan combined with prednisone produces an objective response of 50-60%, although median survival remains approximately 3 years with 5-10% of patients surviving 10 or more years [2]. With the advent of novel targeted agents, the majority of patients have experienced improved survival outcomes in recent years. The immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib are routinely used as first line therapy and have improved the outcomes for myeloma patients. Despite the availability of these newer therapies, the overall prognosis of patients with myeloma remains poor, as patients who do respond to therapy will almost invariably relapse.

1.2 Ixazomib (MLN9708)

1.2.1 Preclinical Experience

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

1.2.2 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 Revlimid and Dexamethasone (RevDex) versus placebo/RevDex. 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. In addition, ongoing clinical pharmacology studies include evaluation of drug-drug interactions with

ketoconazole and rifampin, effect of food, and oral bioavailability. 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 (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.

1.2.3 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.

1.2.4 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 1-1.

Table 1-1 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
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

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
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
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.

1.2.5 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) is shown in Table 1-2.

Table 1-2 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)
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)

Table 1-2 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 (%)
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 1-3). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

Table 1-3 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)
Cough	36 (21)

Table 1-3 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 (%)
Dyspnoea	26 (15)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

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.

Data from ongoing blinded pivotal trials (C16010) are not included.

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

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 [3], non-Hodgkin's disease, Hodgkin's disease [4], relapsed and/or refractory multiple myeloma [RRMM; 5; 6], relapsed or refractory systemic light chain amyloidosis [RRAL; 7], and newly diagnosed multiple myeloma [NDMM; 8; 9; 10]) to date.

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

1.2.6 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.(11, 12) 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.(13, 14, 15) 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.

1.2.7 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. 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.

1.2.8 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).

1.2.9 FDA Approval

In November 2015, the U.S. FDA approved the use of ixazomib in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

The approval was based on an improvement in progression- free survival (PFS) in a multicenter, randomized, double-blind, placebo-controlled trial enrolling 722 patients with multiple myeloma who had received 1 to 3 prior lines of therapy. Patients were randomized in a 1:1 ratio to either the combination of ixazomib, lenalidomide and dexamethasone (n=360) or the combination of placebo, lenalidomide and dexamethasone (n=362). Patients continued treatment until disease progression or unacceptable toxicity.

The trial showed a statistically significant improvement in PFS. The median PFS on the combination arm of ixazomib, lenalidomide and dexamethasone was 20.6 months (95% CI: 17.0, NE) compared to a median PFS of 14.7 months (95% CI: 12.9, 17.6) on the combination arm of placebo, lenalidomide and dexamethasone (PFS HR 0.74, 95% CI: 0.59, 0.94; p value=0.012).

1.3 Value of Minimal Residual Disease Assessment

Historically, the achievement of complete response (CR), defined by absence of monoclonal protein in the serum and urine by immunofixation, along with < 5% bone marrow plasma cells, has been used as the most important determinant to predict outcome following treatment [15-21]. However, in many patients who achieve a complete response, low-level bone marrow disease, so-called minimal residual disease (MRD), can be demonstrated. Several studies have shown that MRD-negativity is a stronger predictor of PFS and OS than conventional CR [29], and thus many new trials are favoring MRD-negativity rate as the primary endpoint over conventional CR rates.

To date, only 5 pubmed searchable studies have analyzed MRD-negative rates post ASCT and the results have varied widely, ranging from 8% to 62% of patients achieving MRD-negative status [22-26]. A meta-analysis of the 5 studies was performed, and of 818 patients analyzed, 416 (51%) achieved MRD-negative status at Day 100 (unpublished data).

Currently there is no consensus way to measure MRD. There are a number of unique panels that utilize multiparameter flow cytometry (MFC) that are currently available or in various stages of testing. Mayo Clinic uses a seven-color panel of antibodies that detect Kappa, Lambda, CD19, CD38, CD45, CD138, and Dapi.

More recently, next generation sequencing techniques have been used to measure MRD, such as Adaptive ClonoSEQ. Adaptive ClonoSEQ involves DNA amplification and sequencing of a bone marrow sample collected prior to the start of treatment. A high-frequency myeloma clone (>5%) is identified and additional samples following the start of treatment are tested using IGH-VDJ_H and IGK or IGH-VDJ_H, IGH-DJ_H, and IGK assays to identify the presence of absence of the original clone. The Adaptive ClonoSEQ technology has been shown to be superior to MFC in predicting response [41], however, its applicability to each patient is dependent on the availability of a pre-treatment bone marrow sample and the identification of high frequency clone.

1.4 Study Rationale

Based on the further need to improve PFS and OS post-ASCT for multiple myeloma and the benefits seen of consolidation/maintenance treatment with immunomodulatory drugs thalidomide and lenalidomide and the proteasome inhibitor bortezomib, the natural next step is to evaluate combination regimens of immunomodulatory drugs and proteasome inhibitors as consolidation/maintenance post-ASCT. The regimen consisting of ixazomib, lenalidomide, and dexamethasone (IRD) has been shown to have low toxicity, and the availability of an oral formulation of ixazomib allows for easier administration when compared to bortezomib.

In this study, following consolidation with IRD, patients will be randomized to maintenance therapy with lenalidomide or ixazomib in order to collect pilot data comparing the toxicity and efficacy of maintenance therapy with immunomodulatory drugs and proteasome inhibitors.

The proposed study would:

1) Provide data on the efficacy and tolerability of IRD as consolidation post ASCT;
2) Provide data on the value of MRD-negativity as a surrogate for PFS and OS;
3) Provide data on the efficacy and tolerability of single agent ixazomib as maintenance therapy post-ASCT;
4) Provide pilot data that could generate hypotheses for a larger phase III study designed to conclusively address the value of IRD consolidation and single agent ixazomib maintenance.

1.4.1 Hypotheses

- Consolidation with 4 cycles of IRD will be well tolerated and will result in ≥ 15% improvement in MRD-negative rate
- MRD-negativity after 4 cycles of IRD consolidation will be associated with an improved PFS and OS
- Maintenance therapy with ixazomib will be well tolerated and will be similar in response rate, PFS, OS, and MRD-positive to MRD-negative conversion rate to maintenance therapy with lenalidomide.

1.4.2 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.

1.5 Correlative Studies Background

The HEVYLITE assay by The Binding Site can identify the different light chain types of each immunoglobulin class ie IgGκ, IgGλ, IgAκ, IgAλ, IgMκ, IgMλ separately, therefore the assay has the potential to identify clonality more precisely than the current assays (SPEP/IF, SFLC, immunoglobulins).

The effect of ixazomib maintenance on the immune system is unknown. In a correlative lab sub-study, we will perform lymphocyte phenotyping and functional assays on peripheral blood samples from 40-50 patients, approximately 20 in each maintenance arm, prior to and post-3 cycles of maintenance.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the improvement in MRD-negative rate after 4 cycles of IRD consolidation.

2.2 Secondary Objectives

1. To determine the MRD-negative rate after ASCT
2. To evaluate the toxicity, response rate, PFS, and OS of IRD consolidation
3. To collect pilot data to compare toxicity, response rate, PFS, OS, and the rate of MRD-positive to MRD-negative conversion between the two maintenance arms
4. To evaluate the association of PFS and OS with MRD-negativity and MRD-positivity prior to consolidation and after 4 cycles of IRD consolidation

2.3 Exploratory Objectives

1. To evaluate the relationship between HEVYLITE assay results with response and MRD status.
2. To evaluate the effect of ixazomib maintenance on the immune system.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to begin IRD Consolidation

1. Between the ages of 18 and 70 years of age (inclusive) at time of enrollment
2. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Histologically confirmed diagnosis of symptomatic multiple myeloma. (Patients with multiple myeloma with secondary amyloidosis are eligible.)
4. Received at least two cycles of any regimen as initial systemic therapy for multiple myeloma and are within 2-16 months of the first dose of initial therapy
5. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2 (see Appendix A).
6. Adequate organ function as defined below:
   - Absolute neutrophil count (ANC) $\geq 1{,}000/mm^3$.
   - Platelet count $\geq 75{,}000/mm^3$; platelet transfusions to help patients meet eligibility criteria are not allowed within 7 days before study enrollment.
   - Total bilirubin $\leq 1.5 \times$ the upper limit of the normal range (ULN).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN.
   - Calculated creatinine clearance ≥ 30 mL/min (see Appendix B).
7. Women of childbearing potential (as defined in Section 5.6) must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material. This is defined as either committing to continued abstinence from heterosexual intercourse or beginning TWO acceptable methods of contraception (one highly effective method and one additional effective method (as defined in Section 5.6) AT THE SAME TIME) at least 28 days prior to the start of lenalidomide, for the duration of study participation, and for 28 days following the last dose of lenalidomide. Women of childbearing potential must also agree to ongoing pregnancy testing.
8. Men must agree to use a latex condom during sexual contact with a woman of childbearing potential even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately**.**

9. All study participants must be registered into the mandatory Revlimid REMS® program and be willing to comply with its requirements. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program**.**

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are lactating or have a positive serum pregnancy test during the screening period.
2. Evidence of MM disease progression any time prior to enrollment. Progression from smoldering/asymptomatic MM to symptomatic MM is not exclusionary.
3. Tandem autologous transplantation
4. History of plasma cell leukemia or MM CNS involvement.
5. Administration or planned administration of any other concomitant chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy which would be considered a treatment of multiple myeloma until Day +28 post-transplant through discontinuation from study. Patients may be on corticosteroids if they are being given for disorders other than multiple myeloma (e.g., adrenal insufficiency, rheumatoid arthritis, etc.).
6. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
7. Prior organ transplant requiring immunosuppressive therapy.
8. Active hepatitis A, B or C virus infection, or known human immunodeficiency virus (HIV) positive.
9. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
10. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib.
11. Concurrent hematologic or non-hematologic malignancy requiring treatment (other than multiple myeloma and secondary amyloidosis).
12. Cardiac syncope, uncompensated NYHA Class 3 or 4 congestive heart failure (Appendix C), myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant repetitive ventricular arrhythmias despite antiarrhythmic treatment, severe orthostatic hypotension, or clinically important autonomic disease.
13. Grade $\geq$ 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period.
14. Major surgery within 14 days prior to start of study treatment.
15. Infection requiring systemic antibiotic therapy or other serious infection within 14 days prior to start of study treatment.

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

3.3 Inclusion of Women and Minorities

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

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Copy of signed consent form (patient name may be blacked out)
2. Planned date of enrollment
3. Completed eligibility checklist, signed and dated by a member of the study team

4.2 Patient Registration in the Siteman Cancer Center Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Overview

In general, patients will provide informed consent prior to ASCT. However, patients may be allowed to provide informed consent following ASCT, determined on a case-by-case basis by the PI. In this event, any of the assessments required prior to ASCT not performed for SOC will not be required.

Patients will undergo standard of care ASCT with conditioning regimen determined by the treating physician per institutional guidelines. The ASCT is not considered part of this study. Consolidation therapy will begin on between Day 80 and Day 120 following ASCT and will consist of four 28-day cycles of IRD (ixazomib, lenalidomide, & dexamethasone). Barring dose modifications for toxicity, 4 mg of ixazomib and 40 mg of dexamethasone will be administered on Days 1, 8, and 15, and 15 mg of lenalidomide will be administered on daily on Days 1-21.

Following completion of consolidation therapy, patients will undergo restaging and will be randomized on a 1:1 basis to maintenance therapy with ixazomib or lenalidomide. Patients will be stratified based on MRD status at restaging (MRD-positive v. MRD-negative). Patients who discontinue either ixazomib or lenalidomide during the consolidation phase due to toxicity will not be randomized. They will be preferentially enrolled on the opposing arm.

Barring dose modifications for toxicity, ixazomib maintenance will consist of 4 mg administered on Days 1, 8 and 15 of each 28-day cycle, and lenalidomide maintenance will consist of 10 mg daily on Days 1-28 for the first three 28-day cycles and 15 mg daily for all further cycles. Maintenance therapy with either ixazomib or lenalidomide will continue until the patient experiences disease progression or unacceptable toxicity.

5.2 IRD Consolidation

5.2.1 Ixazomib Administration

Ixazomib will be prescribed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Ixazomib will be administered on Days 1, 8, and 15 of a 28-day cycle at a starting dose of 4 mg. Sufficient quantity of drug for one cycle of therapy will be prescribed to the patient at a time.

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 6.0). Once ixazomib is reduced for toxicity, no dose re-escalation is permitted.

Ixazomib should be taken on an empty stomach (no food or drink), at least 1 hour before or 2 hours after a meal. Patients should be instructed to swallow ixazomib capsules whole and not to break, chew, or open the capsules. 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.

Ixazomib should be taken at the same time each day. 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. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

5.2.2 Lenalidomide Administration

Lenalidomide will be prescribed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Lenalidomide will be administered daily on Days 1-21 of a 28-day cycle at a starting dose of 15 mg. Sufficient quantity of drug for one cycle of therapy will be prescribed to the patient at a time. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program.

As per standard lenalidomide treatment guidelines, VTE prophylaxis with aspirin 81mg daily should be administered unless the patient is being treated with alternate prophylaxis (Coumadin, low molecular weight heparin, etc) or VTE prophylaxis is contraindicated.

Patients should be monitored for toxicity, as necessary, and doses of lenalidomide should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of lenalidomide dose (see Section 6.0). Once lenalidomide is reduced for toxicity, no dose re-escalation is permitted.

Lenalidomide can be taken without regards to food or drink. Patients should be instructed to swallow lenalidomide capsules whole and not to break, chew, or open the capsules. Each capsule should be swallowed separately with a sip of water.

Lenalidomide should be taken at the same time each day. Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 8 hours or more away. A double dose should not be taken to make up for a missed dose. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

5.2.3 Dexamethasone Administration

Dexamethasone will be prescribed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Dexamethasone will be administered on Days 1, 8, and 15 of a 28-day cycle at a starting dose of 40 mg. Sufficient quantity of drug for one cycle of therapy will be prescribed to the patient at a time.

Patients should be monitored for toxicity, as necessary, and doses of dexamethasone should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of dexamethasone dose (see Section 6.0). Once dexamethasone is reduced for toxicity, no dose re-escalation is permitted.

Dexamethasone should be taken with food or milk. Patients should be instructed to swallow dexamethasone capsules whole and not to break, chew, or open the capsules. Each capsule should be swallowed separately with a sip of water.

Dexamethasone should be taken at the same time each day. Dexamethasone should be taken approximately 1 hour after ixazomib on days when both drugs are being administered.

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. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

5.3 Maintenance Therapy

5.3.1 Randomization

Following completion of consolidation therapy, patients will undergo restaging and will be randomized on a 1:1 basis to maintenance therapy with ixazomib (Arm1) or lenalidomide (Arm2). Patients will be stratified based on MRD status at restaging (MRD-positive vs. MRD-negative). To better ensure the balance of patient characteristics across two arms, treatment assignment will be implemented in small blocks of 4 to 6 patients. The randomization table will be uploaded in our REDCap system. Randomization will occur via an online form with entry of the patient ID number and stratum information. Once all information is entered, randomization is carried out via a submit button through REDCap. The randomization scheme will be created using a formal probability model implemented in SAS (version 9.3 or higher).

5.3.2 Ixazomib Administration

Ixazomib will be prescribed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Ixazomib will be administered on Days 1, 8, and 15 of a 28-day cycle at a starting dose of 4 mg. Sufficient quantity of drug for one cycle of therapy will be prescribed to the patient in Cycles 1-3 of maintenance therapy, and for three cycles of therapy in Cycles 4+.

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 6.0). Once ixazomib is reduced for toxicity, no dose re-escalation is permitted.

Ixazomib should be taken on an empty stomach (no food or drink), at least 1 hour before or 2 hours after a meal. Patients should be instructed to swallow ixazomib capsules whole and not to break, chew, or open the capsules. 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.

Ixazomib should be taken at the same time each day. 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. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

If ixazomib maintenance is discontinued, crossover to the lenalidomide maintenance arm can occur if permission is granted by the Principal Investigator. Patients who crossover will continue to be followed per all protocol guidelines.

5.3.3 Lenalidomide Administration

Lenalidomide will be prescribed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Lenalidomide will be administered daily continuously for a 28-day cycle at a starting dose of 10 mg. If lenalidomide is tolerated well (i.e. no dose modification required) during the first three cycles, lenalidomide dose will be increased to 15 mg daily. Sufficient quantity of drug for one cycle of therapy will be prescribed to the patient in Cycles 1-3, and for three cycles of therapy in Cycles 4+. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program.

VTE prophylaxis is not required during single-agent lenalidomide maintenance but is permissible at the discretion of the treating physician.

Patients should be monitored for toxicity, as necessary, and doses of lenalidomide should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of lenalidomide dose (see Section 6.0).

If a lenalidomide dose reduction has occurred for hematologic toxicity and ANC >1000/µL and platelet count is >75,000/µL, lenalidomide drug dose may be re-escalated one dose level per cycle to a maximum of 15 mg daily. If lenalidomide was reduced due to non-hematologic toxicity, no dose re-escalation is permitted.

Lenalidomide can be taken without regards to food or drink. Patients should be instructed to swallow lenalidomide capsules whole and not to break, chew, or open the capsules. Each capsule should be swallowed separately with a sip of water.

Lenalidomide should be taken at the same time each day. Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 8 hours or more away. A double dose should not be taken to make up for a missed dose. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

If lenalidomide maintenance is discontinued, crossover to the ixazomib maintenance arm can occur if permission is granted by the Principal Investigator. Patients who crossover will continue to be followed per all protocol guidelines.

5.4 Excluded Concomitant Medications and Procedures

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided in this study (14 days before the 1st dose of ixazomib until the final dose of ixazomib), unless there is no appropriate alternative medication for the patient's use. (Rationale: Unlike with inhibitors, 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)
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day

5.5 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- 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.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted, but should not be given prophylactically. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the principal investigator.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Antiviral therapy such as acyclovir may be administered if medically appropriate.
- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery, have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

5.6 Pregnancy Risks – Precautions and Restrictions

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. Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, 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 [e.g., calendar, ovulation,

symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (i.e., 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 [e.g., calendar, ovulation, symptothermal, post-ovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

A woman of childbearing potential is defined as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months. Women of childbearing potential are required to have a negative serum or urine pregnancy test within 10-14 days prior to and again no more than 24 hours before the first dose of lenalidomide. Women of childbearing potential are required to use two forms of contraception at the same time, including one highly effective method (i.e., intrauterine device, hormonal (birth control pills, injections, or implants), tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e., latex condom, diaphragm, cervical cap), from the time of signing of the informed consent form through 90 days after the last dose of study drug. Male patients engaged in a sexual relationship with a woman of childbearing potential must agree to use a latex condom during sexual contact, even if he has had a successful vasectomy.

If a patient is suspected to be pregnant, both study drugs should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

5.7 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

Patients will be removed from the study for any of the following reasons:

- Disease progression or relapse
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

5.8 Duration of Follow-up

Participants will be followed for 18 months after removal from study or until death, whichever occurs first.

6.0 DOSE MODIFICATIONS

Toxicities should be attributed to a specific study drug if possible so that dose modifications can be made rationally. If multiple toxicities are noted, the dose adjustments and or/delays should made once per cycle according to the guidelines for the most severe toxicity. The maximum delay before treatment should be discontinued will be 3 weeks unless permission to resume treatment is granted by the Principal Investigator. Alternative dose modifications than those listed below may be recommended in order to maximize exposure of study treatment while protecting patient safety.

6.1 Dose Levels

Ixazomib Dose Levels

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

Lenalidomide Dose Levels for Consolidation Therapy

Dose Level	Dose (mg)
Starting Dose	15 mg
-1	10 mg
-2	5 mg
-3	Discontinue

Lenalidomide Dose Levels for Maintenance Therapy

Dose Level	Dose (mg)
+1	15 mg
Starting Dose	10 mg
-1	5 mg
-2	5 mg daily for 21 days every 8
-3	Discontinue

Dexamethasone Dose Levels

Dose Level	Dose (mg)
Starting Dose	40 mg
-1	20 mg
-2	8 mg
-3	Discontinue

6.2 Criteria for Beginning a New Treatment Cycle

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

- ANC must be ≥ 1,000/mm^3.
- Platelet count must be ≥ 75,000/mm^3.
- All other treatment related non-hematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the criteria have been met, resume at previous dose levels.

If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate weekly. If a delay of > 2 weeks is required, reduce the suspected drug(s) by one dose level when treatment is resumed. Dosing adjustments should not occur in both ixazomib and lenalidomide simultaneously.

6.3 Dosing Modifications for Hematologic Toxicities

6.3.1 Thrombocytopenia

Only thrombocytopenia determined to be related to one or more study drugs require dose reductions or adjustments as described in this section. Platelet transfusion support is permissible at the discretion of the treating physician. Participants who have treatment delayed for greater than 3 weeks should discontinue protocol therapy.

Dose modifications for thrombocytopenia during IRD Consolidation should be instituted as follows:

Grade	Platelet	Modification
3*	< 50,000/mm^3	**First episode:** Hold **all** drugs until platelets resolve to grade ≤ 1, then reduce lenalidomide by one dose level **Second episode:** Hold **all** drugs until platelets resolve to grade ≤ 1, then reduce ixazomib by one dose level **Third episode:** Hold **all** drugs until platelets resolve to grade ≤ 1, then reduce lenalidomide by one dose level **Fourth episode:** Hold **all** drugs until platelets resolve to grade ≤ 1, then reduce ixazomib by one dose level **Fifth episode:** Discontinue protocol therapy.

Dose modifications for thrombocytopenia during ixazomib or lenalidomide maintenance should be instituted as follows:

Grade	Platelet	Modification
3	< 50,000/mm^3	**First episode:** Hold ixazomib/lenalidomide until platelets resolve to grade ≤ 1, then reduce ixazomib/lenalidomide by one dose level **Second episode:** Hold ixazomib/lenalidomide until platelets resolve to grade ≤ 1, then reduce ixazomib/lenalidomide by one dose level **Third episode:** Hold ixazomib/lenalidomide until platelets resolve to grade ≤ 1, then reduce ixazomib/lenalidomide by one dose level **Fourth episode:** Discontinue protocol therapy.

6.3.2 Neutropenia or Febrile Neutropenia

Only neutropenia/febrile neutropenia determined to be related to one or more study drugs require dose reductions or adjustments as described in this section. Colony-stimulating factor support (such as G-CSF or GM-CSF) for neutropenia is permissible at the discretion of the treating physician, but should not be given prophylactically. Participants who have treatment delayed for greater than 3 weeks should discontinue protocol therapy.

Dose modifications for neutropenia during IRD Consolidation should be instituted as follows:

Grade	ANC	Modification
3	< 1000 /mm^3	**First episode:** Hold **all** drugs until ANC resolves to grade ≤ 1, then reduce lenalidomide by one dose level **Second episode:** Hold **all** drugs until ANC resolves to grade ≤ 1, then reduce lenalidomide by one more dose level **Third episode:** Hold **all** drugs until ANC resolves to grade ≤ 1, then reduce lenalidomide by one more dose level **Fourth episode:** Hold **all** drugs until ANC resolves to grade ≤ 1, then reduce lenalidomide by one more dose level **Fifth episode:** Discontinue protocol therapy.

Dose modifications for neutropenia during ixazomib or lenalidomide maintenance should be instituted as follows:

Grade	ANC	Modification
Dosing Modifications for Non-Hematologic Toxicities		
3	< 1000/mm^3	**First episode:** Hold ixazomib/lenalidomide until ANC resolves to grade ≤ 1, then reduce ixazomib/lenalidomide by one dose level **Second episode:** Hold ixazomib/lenalidomide until ANC resolves to grade ≤ 1, then reduce ixazomib/lenalidomide by one dose level **Third episode:** Hold ixazomib/lenalidomide until ANC resolves to grade ≤ 1, then reduce ixazomib/lenalidomide by one dose level **Fourth episode:** Discontinue protocol therapy.

6.4 Dosing Modifications for Non-Hematologic Toxicities

Dose modification guidelines for treatment related non-hematologic toxicities are as follows:

Toxicity	Grade	Modification
Tumor Lysis Syndrome	Any	**First episode:** Hold **all** drugs until symptoms resolve to baseline, then restart at previous dose levels with appropriate TLS prophylaxis **Second episode:** Discontinue protocol treatment.
Confusion or Mood Alteration	2	**First episode:** Hold dexamethasone until symptoms resolve to baseline, then reduce dexamethasone by one dose level. **Second episode:** Discontinue dexamethasone
Dyspepsia, Gastric or duodenal ulcer, or Gastritis	2	**Each episode:** Treat with histamine-2 blockers, sucralfate, or omeprazole as needed. If symptoms persist despite these measures, decrease dexamethasone by 1 dose level.
Pancreatitis	2	**First episode:** Discontinue dexamethasone.
Peripheral Neuropathy with pain	2	**Each episode:** Hold suspected study drug(s) until toxicity resolves to ≤ grade 1 or baseline, then reduce suspected drug(s) by one dose level.
Muscle Weakness	2	**First episode:** Decrease dexamethasone by one dose level. **Second episode:** If weakness persists, decrease dexamethasone by one more dose level. **Third episode:** Discontinue dexamethasone

Toxicity	Grade	Modification
Rash	2	**Each episode:** Hold suspected study drug(s) until toxicity resolves to ≤ grade 1 or baseline, then restart at previous dose level once at the investigator's discretion.
Thrombosis or Embolism	2	**Each episode:** Hold lenalidomide and commence anticoagulation therapy, then restart at previous dose level at the investigator's discretion.
Diarrhea	3	**Each episode:** Only if the event occurred despite optimal supportive therapy, Hold suspected study drug(s) until toxicity resolves to ≤ grade 1 or baseline, then reduce suspected drug(s) by one dose level.
Dyspepsia, Gastric or duodenal ulcer, or Gastritis	3	**First episode:** Hold dexamethasone until toxicity resolve to ≤ grade 1 or baseline, then decrease dexamethasone by 1 dose level. Prophylactically treat with histamine-2 blockers, sucralfate, or omeprazole as needed. **Second episode:** If symptoms persist despite these measures, discontinue dexamethasone.
Edema	3	**First episode:** Treat with diuretics as needed. Decrease dexamethasone by one dose level. **Second episode:** If edema persists, decrease dexamethasone by one more dose level. **Third episode:** Discontinue dexamethasone
Fatigue	3	**Each episode:** No modification required.
Hyperglycemia	3	**Each episode:** Treat with insulin or hypoglycemic as needed. If uncontrolled despite these measures, decrease dexamethasone by 1 dose level.
Nausea/Vomiting	3	**Each episode:** Only if the event occurred despite optimal anti-emetic prophylaxis, Hold suspected study drug(s) until toxicity resolves to ≤ grade 1 or baseline, then reduce suspected drug(s) by one dose level.
Rash *Exfoliative or bollus rash; Stevens-Johnson Synrome, toxic epidermal necrolysis or Angioedema suspected*	3	**First episode:** Discontinue suspected study drug(s).
Other non-hematologic toxicity	3	**Each episode:** Hold suspected study drug(s) until toxicity resolves to ≤ grade 1 or baseline, then reduce suspected drug(s) by one dose level.

Toxicity	Grade	Modification
Other non-hematologic toxicity	4	**Each episode:** Discontinue protocol therapy unless principal investigator grants permission to continue

6.5 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 6 of the ixazomib IB.

6.5.1 Prophylaxis against Risk of Reactivation of Herpes Infection

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. Other antivirals are also acceptable.

6.5.2 Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

6.5.3 Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

6.5.4 Erythematous Rash With or Without Pruritus

As with bortezomib, 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 ≤ 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 (also, per protocol).

In line with clinical practice, dermatology consult and 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, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

6.5.5 Thrombocytopenia

Blood counts should 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 Table 6-2). 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.

6.5.6 Neutropenia

Blood counts should 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 Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

6.5.7 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.

6.5.8 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.

6.5.9 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.

6.5.10 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.

7.0 PHARMACEUTICAL INFORMATION

7.1 Ixazomib

7.1.1 Description

Ixazomib will be provided by the study in strengths of 4.0, 3.0, and 2.3 mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described 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

For additional details, please see Section 1.2 or refer to the ixazomib IB.

7.1.2 Storage, Handling, and Accountability

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. 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 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 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.

The ixazomib capsules should be stored according to the label. When applicable, the container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C) and patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

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.

7.1.3 Packaging and Labeling

Ixazomib will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

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.

7.1.4 Destruction

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.

7.1.5 Compliance

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.

7.2 Lenalidomide

7.2.1 Lenalidomide Description

Lenalidomide will not be provided by the study. It will be sourced from each patient's commercial pharmacy of choice in accordance with the Celgene Corporation's Revlimid REMS® program.

7.3 Dexamethasone

7.3.1 Description

Dexamethasone will not be provided by the study. It will be sourced from each patient's commercial pharmacy of choice.

8.0 STUDY CALENDAR

Please note that all assessments allow a window of +/-3 days for scheduling issues.

	Screening		**Consolidation[3]**			**Restaging[4]**	**Maintenance[5]**			**EOS[7]**	**F/U[8]**
	Prior to ASCT[1]	Prior to beginning consolidation[2]	D1	D8	D15		D1	D8	D15		
Informed consent	X										
H&P, ECOG PS, plasmacytoma assessment	X	X	X[13]			X	X[13,14]			X	X[15]
CBC & CMP	X		X[13]		X[6]	X	X[13,14]			X	
SPEP and immunofixation	X	X	X[13]			X	X[13,14]			X	
24h urine for total protein, UPEP, and immunofixation[9]	X	X	X[13]			X	X[13,14]			X	
Serum-free light chains & β2 microglobulin	X	X	X[13]			X	X[13,14]			X	
Quantitative immunoglobulins (IgA, IgG, IgM)	X	X	X[13]			X	X[13,14]			X	
Serum βhCG[10]	X	X	X				X			X	
Bone marrow biopsy and aspirate[11]	X	X				X	X[16]				
Central labs[12] (MRD Analysis)		X				X	X[16]				
Central labs[12] (Hevylite)	X		X[13]			X	X[13,14]			X	
Central labs[18] (Sub-study)		X[18]					X[18]				
Ixazomib			X	X	X		X	X	X		
Lenalidomide			Days 1-21				Days 1-28				
Dexamethasone			X	X	X						
Administration Questionnaire[17]			X				X				
Adverse events assessment			X ---------- X								

1. Day -60 to Day -2
2. Day +80 to Day +120; to occur within 28 days prior to C1D1 of consolidation
3. 4 28-day cycles
4. Prior to beginning maintenance (approx. Day +192 to Day +232); to occur within 28 days after completing C4 of consolidation and within 28 days prior to C1D1 of maintenance
5. 28-day cycles; continued until progression or unacceptable toxicity
6. Cycles 1-2 only
7. Within 30 days of last dose of study drug(s)
8. Every 3 months for 18 months
9. Repeat 24h urine only required for patients with ≥ 200 mg/24h of M-protein at screening
10. Women of childbearing potential only; 2 negative tests are required within 14 days before study drug dosing on C1D1 of consolidation
11. Bone marrow aspirate and core biopsy – differential required; Cytogenetics, and fluorescent *in situ* hybridization (FISH) studies performed per institutional guidelines.
12. See Section 9.0
13. Not required on C1D1 if screening/restaging visit occurred within 28 days prior
14. C1-C4 then every 3 cycles thereafter (i.e., C7, C10, C13 …)
15. A telephone call to assess OS and PFS can be made in lieu of a physical exam
16. Cycle 13 for all patients. Cycle 25 and 37 also required for patients in suspected or confirmed CR/sCR at that time.

17. See Appendix D. Patient to complete following each cycle of study treatment (consolidation and maintenance).
18. Only performed on selected patients at Washington University or Ohio State University. See Appendix F.

9.0 CENTRAL LABS

9.1 Mayo Clinic MFC MRD Panel

Approximately 5 ml of bone marrow aspirate in EDTA (pink top) tube(s) will be collected at the following time points:

- Prior to beginning consolidation therapy
- Prior to beginning maintenance therapy
- Cycle 13 Day 1 of maintenance therapy
- Cycle 25 Day 1 of maintenance therapy*
- Cycle 37 Day 1 of maintenance therapy*

*- Only required for patients in suspected or confirmed CR/sCR at that time

9.2 Adaptive ClonoSEQ MRD Testing

If archived bone marrow aspirate or core slides or sections are available from the time of diagnosis or any time prior to study entry, they will be requested.

Additionally, approximately 5 ml of bone marrow aspirate in EDTA (pink top) tube(s) will be collected at the following time points:

- Prior to beginning consolidation therapy
- Prior to beginning maintenance therapy
- Cycle 13 Day 1 of maintenance therapy
- Cycle 25 Day 1 of maintenance therapy*
- Cycle 37 Day 1 of maintenance therapy*

*- Only required for patients in suspected or confirmed CR/sCR at that time

9.3 HEVYLITE Assay

Approximately 10 ml of peripheral blood in serum (red top) tube(s) will be collected at the following time points:

- Prior to ASCT
- Prior to beginning consolidation therapy
- Day 1 of each cycle of consolidation therapy
- Prior to beginning maintenance therapy
- Day 1 C1-C4 of maintenance and then every 3 cycles thereafter
- End of Study

9.4 Handling of Specimen(s)

Instructions for handling and shipment of central labs will be provided in the study lab binder.

9.5 Future Research

Any remaining specimens from blood or marrow after the required correlative studies are completed will be stored for future research including, but not limited to, genetic studies.

10.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section. Electronic data management systems will be used in this trial in collaboration with the Division of Biostatistics at Washington University.

REDCap is a web-based clinical studies data management system that will be used for capture of clinical data from this trial. The case report forms developed for this trial will be transformed to electronic format. An electronic study calendar will drive the study's data collection workflow.

Each participating center has access only to data from its own participants. Washington University, as the data coordinating center, has access to data from all sites. Training in entering data in REDCap is required before a participating center will be given access to the database. In addition, a participating center must have IRB approval of this protocol prior to initiation of REDCap data entry training, which must be completed prior to site study activation.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form Medical History Form Treatment History Form Safety Labs Form MM labs Form Stem Cell Transplant Form	At Baseline
Study Drug Dosing Form Safety Labs Form MM Labs Form Response Form	Each Cycle of Treatment
Bone Marrow Form Response Form	As Per Protocol Requirements
Correlative Studies Form	As Per Protocol Requirements
Adverse Events	Continuous from baseline through safety follow-up visit
MedWatch Form	See Section 8.0 for reporting requirements

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

11.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 11.4.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 11.7. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

11.1 Definitions

11.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

11.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

11.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

11.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

11.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

11.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

11.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

11.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB Pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

11.2 Product Complaints

Definition: 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 MedComm Solutions (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.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed (refer to Section 8.10).

11.3 Medication Error

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact Millennium (see below) and report the event

11.4 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

11.5 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within 10 days of receipt of IRB acknowledgment via email to a QASMC auditor.

11.6 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 11.7) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA.

11.7 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

11.8 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University principal investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 11.1.4) associated with use of the drug by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section11.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

Secondary sites must submit a completed MedWatch form to the Washington University PI and research coordinator within **4 calendar days** (for fatal or life-threatening adverse experiences) or **11 calendar days** (for serious, unexpected adverse experiences). The Washington University PI will be responsible for submitting all MedWatch forms from secondary sites to the FDA within the timeframes specified above.

11.9 Reporting 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).

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 must be reported within 24 hours of the sponsor-investigator's observation or awareness of the event, and all other serious (non-fatal/non life threatening) events must be reported within 4 calendar days of the sponsor-investigator's observation or awareness of the event.

US and Canada Toll-Free Fax #: 1-800-963-6290 E-mail: takedaoncocases@cognizant.com

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue bortezomib. A Pregnancy Form must be requested, completed, and faxed to Millennium Pharmacovigilance. 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, this must be reported to Millennium Pharmacovigilance immediately using the Pregnancy Form. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.10 Timeframe for Reporting Required Events

Adverse events will be collected from first dose of study treatment through the end of study visit.

12.0 MEASUREMENT OF EFFECT

12.1 Response Criteria

Response will be determined by the International Myeloma Working Group (IMWG) Uniform Response Criteria.[36]

12.1.1 Stringent Complete Response

Stringent complete response (sCR) requires all of the following:

- CR as defined below
- Normal free light chain ratio (0.26-1.65)
- Absence of clonal cells in the bone marrow by immunohistochemistry or immunofluorescence

12.1.2 Complete Response

Complete response (CR) requires all of the following:

- Disappearance of monoclonal protein by both protein electrophoresis and immunofixation studies from the blood and urine
- If serum and urine monoclonal protein are unmeasurable, Normal free light chain ratio (0.26-1.65)
- <5% plasma cells in the bone marrow
- Disappearance of soft tissue plasmacytoma

12.1.3 Very Good Partial Response

Very good partial response (VGPR) requires all of the following:

- Serum and urine monoclonal protein detectable by immunofixation but not on electrophoresis
  OR
  ≥ 90% reduction in serum monoclonal protein with urine monoclonal protein < 100 mg per 24 hours
- If serum and urine monoclonal protein are unmeasurable, a ≥ 90% decrease in difference between the involved and uninvolved free light chain levels is required in place of monoclonal protein criteria (The absolute decrease must be > 10 mg/dl)
- If present, > 50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examinations)

12.1.4 Partial Response

Partial response (PR) requires all of the following:

- ≥ 50% reduction in the level of the serum monoclonal protein
- Reduction in urine monoclonal protein by either ≥ 90% or to < 200 mg
- If serum and urine monoclonal protein are unmeasurable, a ≥50% decrease in difference between the involved and uninvolved free light chain levels is required in place of monoclonal protein criteria (The absolute decrease must be > 10 mg/dl)
- If serum and urine monoclonal protein are unmeasurable and serum free light chain is unmeasurable, a ≥ 50% reduction in plasma cells is required in place of monoclonal protein, provided that baseline bone marrow plasma cell percentage was ≥ 30%
- If present, > 50% reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examinations).

12.1.5 Stable Disease

Stable disease (SD) is defined as not meeting criteria for any other response as defined in this section.

12.1.6 Progressive Disease or Clinical Relapse

Progressive disease (PD) requires one or more of the following:

- $\geq$ 25% increase in the level of serum monoclonal protein, which must also be an absolute increase of at least 0.5 g/dL and confirmed on a repeat investigation
- $\geq$ 25% increase in 24-hour urine monoclonal protein, which must also be an absolute increase of at least 200 mg/24hr and confirmed on a repeat investigation.
- If serum and urine monoclonal protein are unmeasurable, $\geq$ 25% increase in the difference between involved and uninvolved free light chain levels, which must also be an absolute increase of at least 10 mg/dL and confirmed on a repeat investigation
- $\geq$ 25% increase 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. A definite increase is defined as at least 50% (and at least 1 cm) increase as measured serially as the sum of the products of the cross-diameters of the lesions.
- Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture).
- Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L not attributable to any cause other than progressive multiple myeloma).
- Decrease in hemoglobin > 2 g/dl not attributable to any cause other than progressive multiple myeloma
- Increase in creatinine by > 2 mg/dl not attributable to any cause other than progressive multiple myeloma
- Other worsening laboratory result, or clinical condition that the treating physician determines is not attributable to any cause other than progressive multiple myeloma

Note: A response of progressive disease/clinical relapse nullifies any other concurrent response. For example, at a given time point a participant meets criteria for VGPR but has development of new bone lesions the response is PD not VGPR.

12.1.7 Relapse from Complete Response

Relapse from a complete response requires a prior CR or sCR as described above and subsequently developing one or more of the following:

- Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis excluding oligoclonal immune reconstitution, and confirmed on a repeat investigation
- Development of $\geq$ 5% plasma cells in the bone marrow aspirate or biopsy.
- Appearance of any sign of progressive disease or clinical relapse as stated above.

12.2 Minimal Residual Disease

For the purposes of this study, a patient will be considered as having minimal residual diseases if a positive result is obtained using the Adaptive Clonoseq MRD testing. In the event that Adaptive Clonoseq cannot be performed, a patient will be considered as having minimal residual diseases if a positive result is obtained using the Mayo MFC MRD Panel.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Data and Safety Monitoring Committee (DSMC) will meet to review toxicity data at least every 6 months following the activation of the first secondary site. The report will be prepared by the statistician with assistance from the study team and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site, and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy

- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites and separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

14.0 AUDITING

Since Washington University is the coordinating center, each site will be audited annually by Siteman Cancer Center personnel (QASMC) unless the outside institution has an auditing mechanism in place and can provide a report. The outside sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Additional details regarding the Auditing Policies and procedures can be found at http://www.siteman.wustl.edu/uploadedFiles/Research_Programs/Clinical_Research_Resources/Protocol_Review_and_Monitoring_Committee/QASMCQualityAssurcance.pdf

15.0 STATISTICAL CONSIDERATIONS

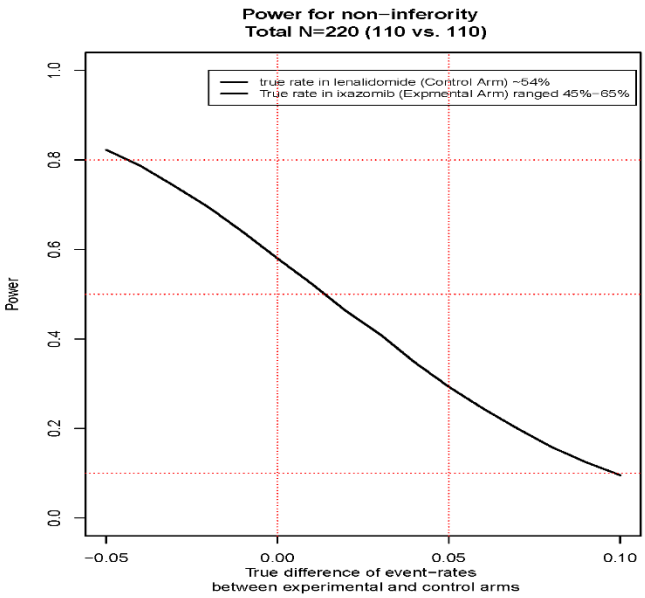
This is an open-label, randomized phase II study that will accrue at 4-6 centers within the United States. The total accrual goal is 220 patients evaluable for the primary objective. We estimate the percentage of patients treated that will be evaluable for the primary objective to be > 90%, thus a total accrual of up to ~~240 patients may be needed. The estimated accrual is 10-12 patients per month, with a projected enrollment time frame of 24 months.

15.1 Determination of Sample Size

A power analysis was performed for the primary objective. The smallest increase in MRD-negative rate after four cycles of IRD that would warrant further investigation is 10%, with a result of $\leq$ 9% being considered ineffective. Based on a meta-analysis of five prior studies in this population, the expected MRD-negative rate at Day 100 post-transplant is ~50%. If the true rate of MRD-negative is 40-60% at the Day 100 post-transplant visit, 220 evaluable patients will detect a 10% improvement in MRD-negative rate with 90% power at 1-sided 0.05 alpha. Due to highly varied data of baseline MRD (i.e., 5 published studies showed MRD-negative rates ranged from 8% to 62%) as well as the lack of pilot information for the association over time, we currently choose a rather conservative estimation and the sample size is estimated using non-paired design instead. However, an interim analysis will be performed when ~50 patients are randomized to maintenance arms, and sample size adjustment will then be made if needed (see details below for interim analysis).

The randomized maintenance portion of the study will provide pilot data that will be used to design future studies. Although the study was not powered to show non-inferiority or superiority of either of the two maintenance arms, the designed sample size (n=110 evaluable patients/arm) will provide us a reasonable power for our hypothesis that "Maintenance therapy with ixazomib will be well tolerated and will be similar in response rate, PFS, OS, and MRD-positive to MRD-negative conversion rate to maintenance therapy with lenalidomide". Taking PFS as an example, the recent meta-analysis of lenalidomide versus placebo/observation showed that the 5-year cumulative incidence of events (PD or 2nd-line treatment) was ~54%. [29] The figure below illustrates the statistical power to show non-inferiority given the “true” difference of event rates (e.g., death or recurrence or treatment failure) between the ixazomib arm (experimental group) and lenalidomide arm (control group). With a non-inferiority margin of 10% in 5-year PFS (or equivalently a hazard ratio (HR) of 1.3), for example, the designed sample size would allow 80% power to claim non-inferiority when a slightly better PFS is observed in the ixazomib arm.

This power analysis was based on a simulation study where



- the true rate in the experimental treatment (ixazomib) varied from 45% to 65%;
- the true recurrence rate in the control (lenalidomide) varied from 52% to 56%;
- a total of 10,000 replicates are generated under each scenario, and each replicate includes N=110 ixazomib patients and N=110 lenalidomide patients;
- events in each arm were generated following binomial distributions;
- 1-sided 90% confidence interval (CI) for the difference between event rates was calculated and non-inferiority will be declared if the upper boundary of CI is below 10% [30]. That is, the non-inferiority margin was set as 10% absolute difference, or equivalently a hazard ratio (HR) of 1.3 when assuming the time following an exponential distribution;
- The figure shows average power as a function of the true difference of event rates between experimental and control groups;
- Note that the current simulation was based on binary data for simplicity. We expect that more power could be achieved in the actual time-to-event analysis due to the availability of richer information (i.e., not only the status of event, but also the exact time when it happens).

The accrual rate over six participating centers will be roughly 6 patients per month, with a total accrual timeframe of about 3 years following study activation.

15.2 Randomization and Stratification

Following initial treatment with IRD consolidation therapy, patients will be randomized to a pilot portion of the study evaluating ixazomib or lenalidomide as maintenance therapy.

Patients will be restaged following completion of consolidation treatment and will be randomized on a 1:1 basis to maintenance therapy with ixazomib or lenalidomide. Patients will be stratified based on MRD status at restaging (MRD-negative v. MRD-positive). For the purposes of randomization, if there are discrepant results from the Mayo Clinic MFC and the Adaptive ClonoSEQ MRD tests, the Adaptive ClonoSEQ results will be used for stratification. In the event that the Adaptive ClonoSEQ results are not available, the Mayo Clinic MFC results will be used for stratification, and vice versa.

15.3 Data Analysis

For the analysis of consolidation therapy, the data for safety analysis will include these patients who have at least 1 dose of IRD consolidation therapy, while the data for efficacy analysis will include patients who complete 4 cycles therapy. Demographic and clinical characteristics of the sample, as well as adverse events, complications and loss to follow-up will be summarized using descriptive statistics. The change of MRD-negative rates for pre- and post-consolidation therapy will be described using contingency table and compared by McNemar test. The incidences of mortality, progression, relapse, as well as tumor response (complete response and overall) and their 95% confidence intervals following consolidation therapy will also be calculated.

Data analysis for maintenance portion will be performed following the intent-to-treat (ITT) principle. The balance of demographic and baseline clinical characteristics between two arms will be compared using t-test, Mann-Whitney rank-sum test, or Chi-square test as appropriate. The distributions of responses and adverse events across two arms will be summarized using contingency tables and compared by 2-sample Chi-square test or Fisher's exact test. Contingency table and Fisher's exact test will also be used to assess the between-arms difference for the rates of conversion from MRD-positive to MRD-negative. Chi-square test will be used to compare the distribution of responses, and Kaplan-Meier curves with log rank tests will be used to compare PFS and OS.

Overall survival (OS) will be defined as time from ASCT to death due to any causes, and survivors will be censored at withdrawal or study closeout. Progression-free survival (PFS) will be defined as time from ASCT to progression, relapse, or death, whichever occurs first, and those event-free survivors will be censored at withdrawal or study closeout. The between-arm differences in OS and PFS will be described using Kaplan-Meier product limit estimator and compared by log-rank tests. Kaplan-Meier curves will also be used to describe the association between MRD status (both prior to and after consolidation therapy) and OS or PFS, and proportional hazards Cox models will be used to control the potential confounding effects of other patient and clinical characteristics.

15.4 Interim Analysis

Two interim analyses will be performed during the consolidation phase of the trial. The first will occur when ~50 patients complete the consolidation therapy and are randomized to maintenance portion. The second will occur in Year-3, after approximately 150 evaluable patients complete the consolidation therapy and are randomized to maintenance portion.

The data analysis will be descriptive in nature. The change of MRD-negative rates for pre- and post-consolidation therapy will be estimated using contingency table. Sample size will be re-estimated and conditional power will also be calculated based on the accumulated data. Conditional power is defined as the projected power to reject the null hypothesis at the end of study given the data accrued up to a specific interim analysis.

Therefore, a high value of conditional power indicates a highly likely, if not inevitable, conclusion to reject the null hypothesis given the available information. Similarly, a small value suggests a high possibility of negative finding given the current data. This interim analysis will assist investigators on the decision whether the sample size (220 evaluable, ~240 total) needs to be adjusted.

Two additional interim analyses will also be scheduled to monitor the futility of maintenance portion and thus to reduce the exposure of patients to inferior treatment. The first will occur in Year-4 (i.e., near the end of accrual period) and the other at Year-6 (i.e., when all patients have at least 2-year follow-up of maintenance therapy). Each interim analysis will be descriptive in nature. The rates of conversion from MRD-positive to MRD-negative across different arms will be summarized using contingency tables and compared by Fisher's exact test. The differences in PFS or OS between arms will be described using hazard ratios (HR). Kaplan-Meier product limit method will also be used to estimate survival curves and the corresponding confidence intervals. The stopping rule for an early termination due to futility will follow the guidelines for non-inferiority trials. [31] That is, the study will be recommended for an early termination whenever the observed HR is equal or worse than 1.3 (the non-inferiority margin) and the outcome is in favor of lenalidomide (control arm). For PFS, for example, the recent meta-analysis showed that the 1-year and 2-year event rates in the lenalidomide cohort are 13% and 25%, respectively, and HR=1.3 corresponds to an increase of ~3% and ~6% for 1-year and 2-year event rates.

16.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Each participating institution must have the following documents on file at Washington University prior to first subject enrollment:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution’s IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572, and signed and dated CVs of all participating investigators.
- Documentation of training in protection of human subjects by all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The Principal Investigator is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. There will be one current version of the protocol document at any given time and each participating institution will utilize that document. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 2 weeks of obtaining Washington University IRB approval with acknowledgement of receipt requested. Secondary sites are to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt, and confirmation of submission must be forwarded to the appropriate contact person on the Washington University study team at the time of submission. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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APPENDIX A: ECOG Performance Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140 - \text{age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\,(140 - \text{age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\,(140 - \text{age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

APPENDIX C: New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX D: Administration Questionnaire: Consolidation Cycle _____

What dose of ixazomib were you prescribed for this cycle of treatment?
(check all that apply)

4.0 mg on Days 1, 8, & 15
3.0 mg on Days 1, 8, & 15
2.3 mg on Days 1, 8, & 15
None

What dose of lenalidomide were you prescribed for this cycle of treatment?
(check all that apply)

15 mg on Days 1-21
10 mg on Days 1-21
5 mg on Days 1-21
None

What dose of dexamethasone were you prescribed for this cycle of treatment?
(check all that apply)

40 mg on Days 1, 8, & 15
20 mg on Days 1, 8, & 15
8 mg on Days 1, 8, & 15
None

Did you take all of the prescribed doses? (circle one) Yes No

If No, please explain:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Patient Initials _____ Date_____

APPENDIX E: Administration Questionnaire: Maintenance Cycle _____

What dose of ixazomib were you prescribed for this cycle of treatment?
(check all that apply)

4.0 mg on Days 1, 8, & 15
3.0 mg on Days 1, 8, & 15
2.3 mg on Days 1, 8, & 15
None

What dose of lenalidomide were you prescribed for this cycle of treatment?
(check all that apply)

15 mg on Days 1-28
10 mg on Days 1-28
5 mg on Days 1-28
5 mg on Days 1-21
None

Did you take all of the prescribed doses? (circle one) Yes No

If No, please explain:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Patient Initials _____ Date_____

APPENDIX F: Correlative Sub-study

Up to 50 patients (approximately 20 in each maintenance arm) will provide informed consent to the optional correlative sub-study to study the effect of ixazomib maintenance on the immune system.

Approximately 20 ml of peripheral blood in EDTA (pink top) tube(s) will be collected at the following time points:

- Prior to beginning consolidation therapy
- Cycle 1 Day 1 of maintenance (pre-drug)
- Cycle 4 Day 1 of maintenance (pre-drug)

Instructions for handling and shipment of samples will be provided in the study lab binder. Lymphocyte phenotyping and functional assays will be performed at the conclusion of the correlative sub-study.